The American Journal of Cardiology

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OCTOBER 15, 1990

19.4.91

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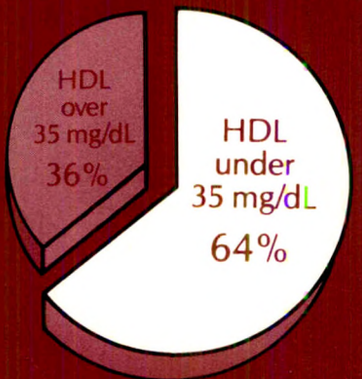
270 TOTAL

<35 HDL mg/dL

What's a common denominator of most heart attack victims?

Mixed hyperlipidemias—elevated cholesterol *and* triglycerides—are common among heart attack victims,[1] and nearly two-thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.[2]

HEART ATTACK PATIENTS
(PROCAM TRIAL)[2]



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A powerful case for LOPID® (gemfibrozil)



BID 600-mg Tablets

Raised low HDL 25%

—in patients whose baseline HDL was below 35 mg/dL in the landmark Helsinki Heart Study (HHS).[3]

Reduced heart attack incidence* up to 62%

—in these HHS patients and 45% in HHS patients whose baseline HDL was below the median (46.4 mg/dL). Incidence of serious coronary events was similar for LOPID and placebo subgroups with baseline HDL above the median (46.4 mg/dL).[3]

Raised HDL levels 1½ to 3 times more effectively than lovastatin

—in a 12-week, double-blind, randomized trial among patients with moderate to severe hyperlipidemia. Lovastatin achieved greater reductions in total serum cholesterol than gemfibrozil in this study population.[4]

RAISES HDL DRAMATICALLY REDUCES HEART ATTACK

LOPID is indicated for reducing the risk of coronary heart disease (CHD) in Type IIb patients with low HDL, in addition to elevated LDL and triglycerides, and who have had an inadequate response to weight loss, diet, exercise, and other pharmacologic agents such as bile acid sequestrants and nicotinic acid.

*Defined as a combination of definite coronary death and/or definite myocardial infarction.

References: 1. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. *J Clin Invest.* 1973;52:1533-1543. **2.** Assmann G, Schulte H. *PROCAM-Trial: Prospective Cardiovascular Münster Trial.* Zürich: Panscientia Verlag; 1986:8-9. **3.** Data on file, Medical Affairs Dept, Parke-Davis **4.** Tikkanen MJ, Helve E, Jäättelä A, et al. Comparison between lovastatin and gemfibrozil in the treatment of primary hypercholesterolemia: the Finnish Multicenter Study. *Am J Cardiol.* 1988;62:35J-43J.

Please see last page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

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Before prescribing, please see full prescribing information.
A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

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(gemfibrozil) 600-mg Tablets
RAISES HDL...DRAMATICALLY
REDUCES HEART ATTACK

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts—Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy**—Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy**—Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions**—(A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility**—Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

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from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children**—Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

References: 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-1245. 2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651. 3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J. B. et al. (eds.) *The Metabolic Basis of Inherited Disease*, 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642.

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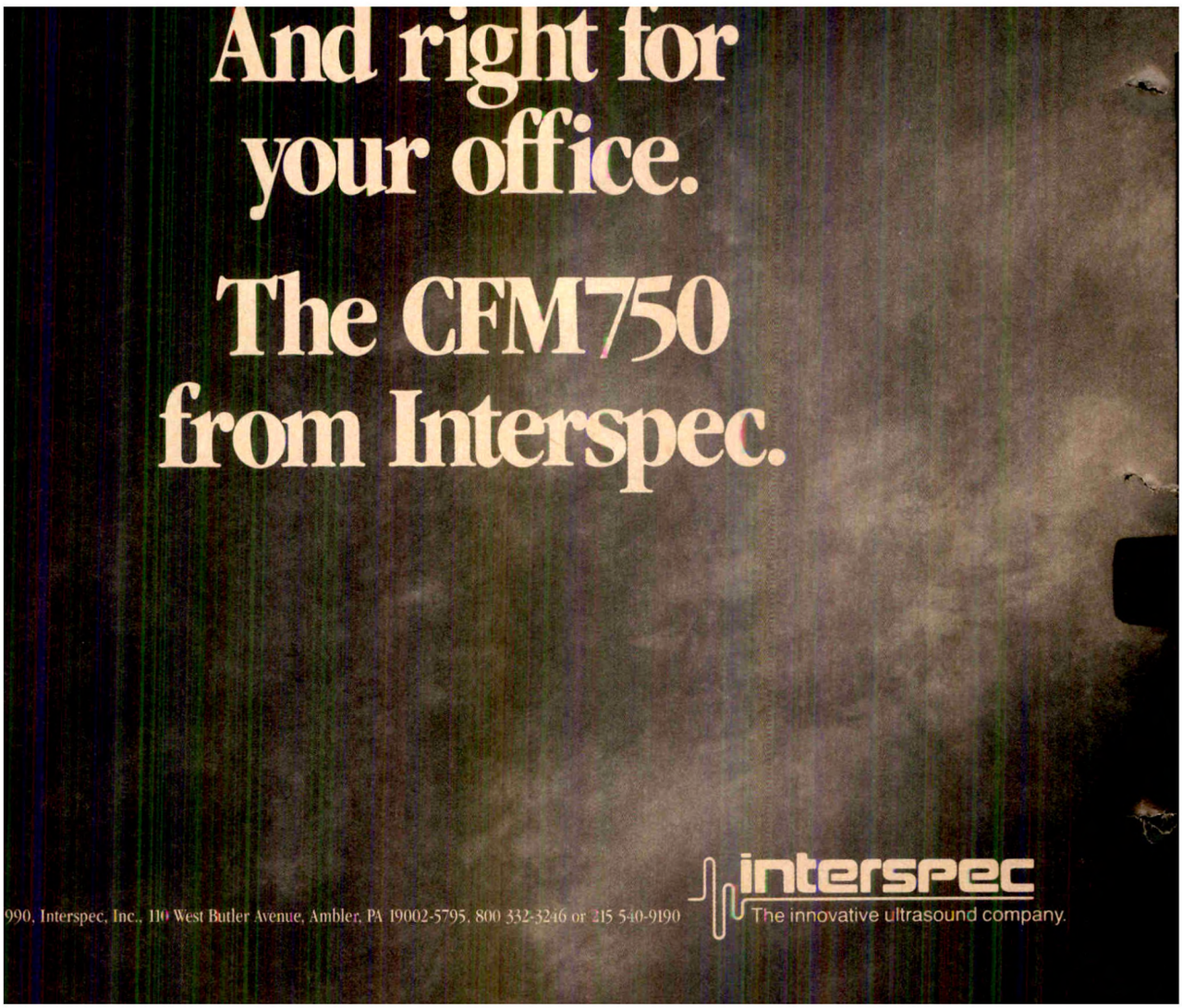
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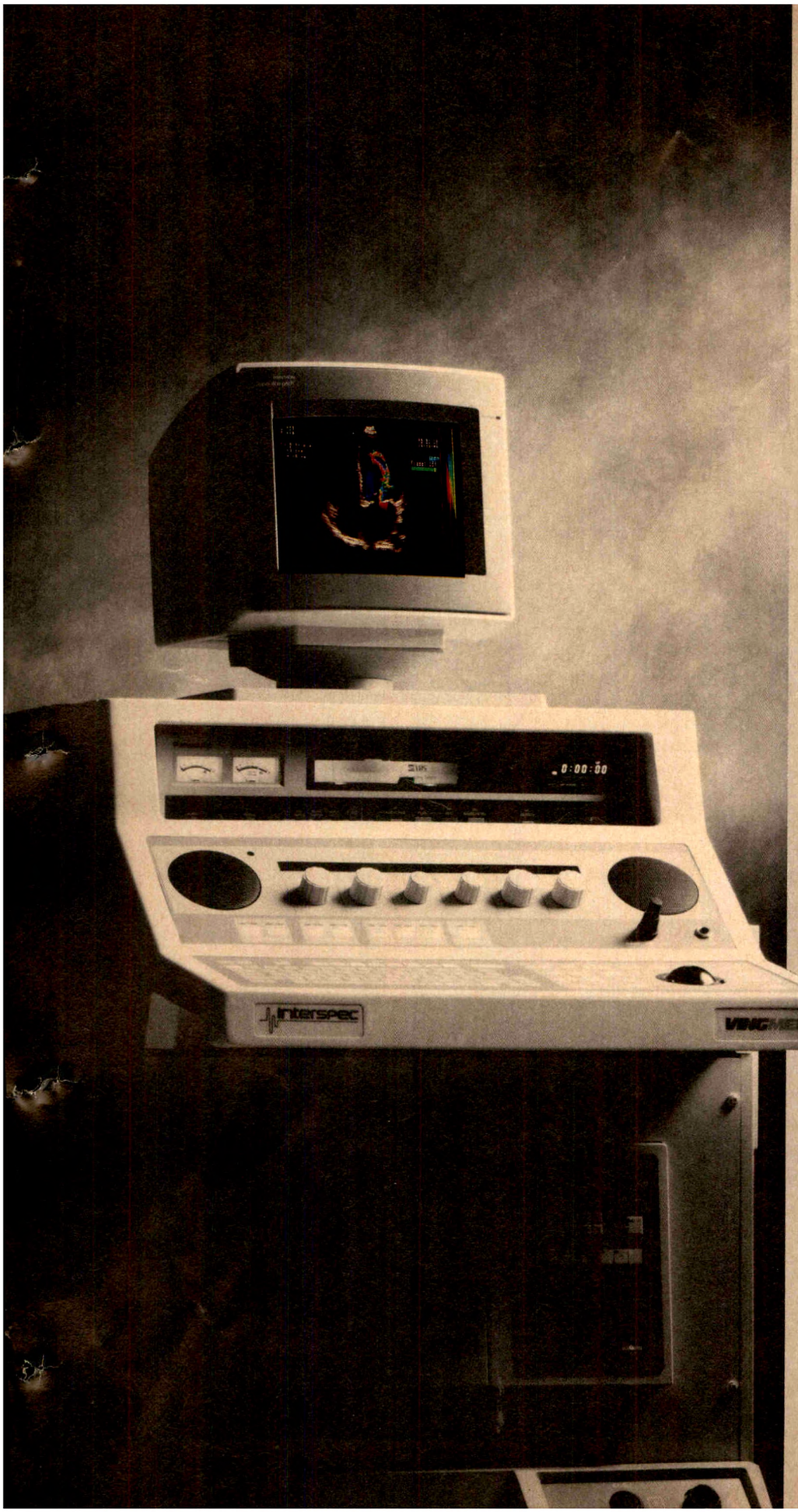
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CORONARY ARTERY DISEASE

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Transient Left Ventricular Filling Abnormalities (Diastolic Stunning) After Acute Myocardial Infarction
Brian D. Williamson, Michael J. Lim, and Andrew J. Buda

To examine diastolic filling after acute myocardial infarction, Doppler echocardiograms were performed in 60 patients within 24 hours of infarction and again 7 days after infarction in a subgroup of 17 patients; 15 patients with stable coronary artery disease served as control subjects. Our data indicate that left ventricular filling is further impaired during acute infarction, with the predominant impairment in early diastole. After infarction, filling parameters improve over the first 7 days after infarction, suggesting a recovery of diastolic stunning.

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Comparison of Coronary and Myocardial Morphologic Findings in Patients With and Without Thrombolytic Therapy During Fatal First Acute Myocardial Infarction
S. David Gertz, Amy H. Kragel, Jay M. Kalan, Eugene Braunwald, William C. Roberts, and The TIMI Investigators

The hearts of 61 patients after a fatal first acute myocardial infarction without percutaneous transluminal coronary angioplasty or coronary artery bypass grafting were studied. Patients who received tissue-plasminogen activator had greater frequency of nonocclusive thrombi with a lower frequency of infarct-related arteries obstructed by the thrombus at necropsy and a lower frequency of myocardial rupture.

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Recombinant Tissue-Type Plasminogen Activator Followed by Heparin Compared with Heparin Alone for Refractory Unstable Angina Pectoris
Diego Ardissino, Paolo Barberis, Stefano De Servi, Antonio Mussini, Alberto Rolla, Luigi Visani, and Giuseppe Specchia

Twenty-four patients with unstable angina refractory to conventional medical treatment underwent a randomized, double-blind trial to assess and compare short-term efficacy of treatment with recombinant tissue-type plasminogen activator followed by heparin and treatment with heparin alone. This study shows that the combination of rt-PA and heparin has a greater protective effect than heparin alone in treating such patients.

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Role of Beta-Adrenergic Blockers After Percutaneous Transluminal Coronary Angioplasty
Sten R. Johansson, Carl Lamm, Göran Bondjers, Håkan Emanuelsson, and Åke Hjalmarson

We evaluated 541 consecutive percutaneous transluminal coronary angioplasty procedures where 86% of the patients were treated with β blockers. Our results indicate that treatment with β blockers after PTCA does not influence success or restenosis rates and can be continued if indicated from an antiischemic viewpoint.

921
Functional Status After Coronary Artery Bypass Grafting and Percutaneous Transluminal Coronary Angioplasty
Jerilyn K. Allen, Sheila T. Fitzgerald, Robert T. Swank, and Diane M. Becker

To examine functional status outcomes during the first year of recovery, we performed a prospective study of 2 cohorts of patients of comparable age with similar preprocedure cardiac function who underwent either coronary artery bypass grafting or percutaneous transluminal coronary angioplasty. Measures of psychological and work functioning indicated better functioning after CABG than after PTCA; whereas the CABG group experienced significant improvements in all dimensions of functional status, the PTCA group demonstrated significant improvement in all dimensions except for the quality of social interaction.

926
Patient-Related Variables and Restenosis After Percutaneous Transluminal Coronary Angioplasty—A Report from the M-HEART Group
Robert G. Macdonald, Mark A. Henderson, John W. Hirshfeld, Jr., Sheldon H. Goldberg, Theodore Bass, George Vetrovec, Michael Cowley, Andrew Taussig, Hall Whitworth, James R. Margolis, James A. Hill, Ralph Jugo, and Carl J. Pepine for the M-HEART Group

As part of a multicenter restenosis trial (M-HEART) we prospectively collected data to determine whether there is an association between patient-related variables and risk of restenosis after coronary angioplasty. An angiographic restudy was performed in 510 patients (71%), providing 598 dilated lesions for analysis. None of the variables analyzed had a statistically significant association with restenosis.

932
Results of Percutaneous Transluminal Coronary Angioplasty of High-Risk Angulated Stenoses
Stephen G. Ellis and Eric J. Topol

We characterized 100 sequentially treated patients from 1986 to 1989 undergoing percutaneous transluminal coronary angioplasty of stenoses located at $\geq 45°$ bends for 27 clinical, anatomic and procedural variables, and related the clinical outcome of PTCA to these variables. PTCA of such stenoses should be undertaken only cautiously and in carefully selected patients.

938

Quantitative Angiographic Comparison of the Immediate Success of Coronary Angioplasty, Coronary Atherectomy and Endoluminal Stenting

David W. M. Muller, Stephen G. Ellis, Darrell L. Debowey, and Eric J. Topol

We quantitatively evaluated pre- and postprocedural coronary angiograms in 18 patients undergoing coronary atherectomy, in 21 patients treated by endoluminal coronary stenting and in 39 matched patients undergoing coronary balloon angioplasty. Our findings suggest that, in selected patients, coronary atherectomy or stenting may be preferable to conventional balloon angioplasty.

943

Early Postoperative Balloon Coronary Angioplasty for Failed Coronary Artery Bypass Grafting

Joel K. Kahn, Barry D. Rutherford, David R. McConahay, Lee V. Giorgi, Warren L. Johnson, Thomas M. Shimshak, and Geoffrey O. Hartzler

To examine the usefulness of early coronary angioplasty for the treatment of recurrent ischemia after coronary artery bypass grafting, we treated 45 patients from 2 to 90 days after CABG. Percutaneous transluminal coronary angioplasty can relieve myocardial ischemia after failed CABG in the majority of patients.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

947

Electrophysiologic and Electrocardiographic Effects, Efficacy and Safety of Encainide in Malignant Ventricular Arrhythmias Associated with Coronary Artery Disease

Andrew R. Weintraub, Antonis S. Manolis, and N.A. Mark Estes III

How effective and safe is encainide in patients with potentially fatal ventricular tachyarrhythmias? Using electrophysiologic testing, we evaluated the electrocardiographic and electrophysiologic effects in 48 patients with coronary artery disease.

954

Role of Alcohol in Recurrences of Atrial Fibrillation in Persons <65 Years of Age

Pekka Koskinen, Markku Kupari, and Hannu Leinonen

We examined the etiologic role of alcohol in recurrences of atrial fibrillation in 98 consecutive patients <65 years of age. Compared to 98 age- and sex-matched hospital control subjects, AF patients had consumed significantly more alcohol during the week preceding the arrhythmia. Multivariate analysis of data on AF patients and 50 randomly selected out-of-hospital control subjects showed that alcohol intake and a positive response to 1 or more of the CAGE questions (a screening test for alcohol abuse) were related, independently of serum potassium, associated disease and stress or lack of sleep, to AF in men.

959

Circadian Rhythmicity of Rate-Normalized QT Interval in Hypothyroidism and Its Significance for Development of Class III Antiarrhythmic Agents

Jonnalagedda S. M. Sarma, Kalyanasundaram Venkataraman, Pascal Nicod, Ralf Polikar, Johana Smith, Mary P. Schoenbaum, and Bramah N. Singh

Can the circadian rhythmicity of QTc length in hypothyroid patients, prolonged even after thyroxine replacement restored thyroid plasma values to normal, reveal significant information about how new class III antiarrhythmic agents might be developed for the control of ventricular arrhythmias in normally euthyroid patients with cardiovascular disorders? We used a new computer technique to help determine that the circadian rhythms of QTc length are qualitatively similar among hypothyroid, newly euthyroid, and normally euthyroid people.

964

Chronic Transvenous Pacemaker Lead Removal Using a Unique, Sequential Transvenous System

George K. Brodell, Lon W. Castle, James D. Maloney, and Bruce L. Wilkoff

Transvenous removal of 43 consecutive pacemaker leads was successful in 28 patients. A unique locking stylet and telescoping sheaths are used to provide consistent results.

SYSTEMIC HYPERTENSION

967

Comparison of the Antihypertensive Efficiency of Nitrendipine, Metoprolol, Mepindolol and Enalapril Using Ambulatory 24-Hour Blood Pressure Monitoring

Joachim Schrader, Gerhard Schoel, Heike Buhr-Schinner, Michael Kandt, Gerhard Warneke, Victor W. Armstrong, and Fritz Scheler

In a randomized 6-month study on 201 patients, the antihypertensive efficiency of nitrendipine, metoprolol, mepindolol and enalapril was compared as monitored by 24-hour ambulatory blood pressure measurements. Despite comparable casual BP control, the 4 groups differed significantly in their mean 24-hour measurements. The greatest systolic and diastolic blood pressure decreases were seen in the metoprolol group; metoprolol was also the most effective drug in decreasing the frequency of systolic pressure peaks >180 mm Hg.

CONGESTIVE HEART FAILURE

973

Expression of Natriuretic Peptide in Ventricular Myocardium of Failing Human Hearts and Its Correlation with the Severity of Clinical and Hemodynamic Impairment

Eloisa Arbustini, Angela Pucci, Maurizia Grasso, Marta Diegoli, Roberto Pozzi, Antonello Gavazzi, Gabriella Graziano, Carlo Campana, Claudio Goggi, Luigi Martinelli, Enrico Silini, Giuseppe Specchia, Mario Vigano, and Enrico Solcia

Atrial natriuretic peptide was immunohistochemically investigated in (1) right ventricular endomyocardial biopsy specimens from 87 apparently healthy donor hearts; (2) 1 normal heart not suitable for transplantation; (3) right ventricular endomyocardial biopsy specimens from 151 patients with dilated cardiomyopathy; and (4) 57 explanted hearts. Healthy ventricles do not express ANP immunoreactivity, whereas failing ventricles do. Venticular ANP reactivity seems to be unrelated to the underlying disease, but strictly dependent on the degree of left ventricular dysfunction.

981

Usefulness of Verapamil for Congestive Heart Failure Associated with Abnormal Left Ventricular Diastolic Filling and Normal Left Ventricular Systolic Performance

John F. Setaro, Barry L. Zaret, Douglas S. Schulman, Henry R. Black, and Robert Soufer

We studied 20 men in a prospective, double-blind, placebo-controlled, crossover trial to determine the therapeutic efficacy of verapamil in congestive heart failure patients whose left ventricular systolic function is preserved, but whose diastolic function is abnormal.

987
Changes in Circulating Norepinephrine with Hemofiltration in Advanced Congestive Heart Failure
Carlo M. Cipolla, Sergio Grazi, Andrea Rimondini, Giuseppe Susini, Marco Guazzi, Paolo Della Bella, and Maurizio D. Guazzi

In cases of advanced congestive heart failure with fluid retention, filtration of plasma water (2,983 ml) greatly decreased elevated levels of plasma norepinephrine. Despite this, the associated hemodynamic variations were negligible, suggesting that in CHF the elevation of the circulating sympathetic transmitter does not contribute significantly to the hemodynamic control and probably does not reflect the intensity of the neural activity. Our data indicate that a reduced clearance of norepinephrine due to retention of fluid may importantly contribute to the increase of circulating norepinephrine in CHF.

MISCELLANEOUS

995
Effects of Preload Reduction on Mitral Flow Velocity Pattern in Normal Subjects
Marco O. Triulzi, Diego Castini, Maurizio Ornaghi, and Erminio Vitolo

To evaluate the effects of systemic venous return reduction on mitral flow velocities by Doppler echocardiography, we studied 12 normal subjects in the basal state and after a 5-minute period of pressure cuffs inflation on the 4 limbs. We observed a significant decrease of peak E-wave velocity with no significant changes of the peak A-wave velocity; this resulted in a significant reduction of the E/A peak velocity. Thus, preload reduction in normal subjects determines a mitral flow velocity pattern that mimics the changes already observed in left ventricular diastolic dysfunction.

1002
Clinical and Hemodynamic Assessment of the Hepatojugular Reflux
Randall A. Sochowski, James D. Dubbin, and Salim Z. Naqvi

Sixty-five patients without heart failure underwent hepatojugular reflux testing at the bedside and during cardiac catheterization to determine the test's significance in this patient population. A positive test can detect elevated right-sided cardiac pressures and correlated best to baseline mean right atrial and right ventricular end-diastolic pressures. This suggests a central role of right-sided cardiac function in determining the response.

METHODS

1007
Anatomic Correlations of the Long-Axis Views in Biplane Transesophageal Echocardiography
Gerald I. Cohen, Kwan-Leung Chan, and Virginia M. Walley

We assessed use of the long-axis plane of the biplane probe in providing long-axis views in ambulatory patients. Six standard long-axis views were compared with corresponding anatomic sections to illustrate anatomic relations and facilitate structure identification.

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Circadian Fluctuations in Ventricular Response to Atrial Fibrillation
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Noninvasive Evaluation of Left Ventricular Performance with a New Systolic Time Interval, the Q-V Peak, and Comparison with Established Systolic Time Intervals
Nobuyuki Ohte, Takeshi Hashimoto, Hitomi Narita, Rie Takase, Kenji Kobayashi, Junichiro Hayano, and Takao Fujinami

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Selective Infusion of Thrombolytic Therapy in the Acute Myocardial Infarct-Related Coronary Artery as an Alternative to Rescue Percutaneous Transluminal Coronary Angioplasty
Paul A. Gurbel, Charles J. Davidson, E. Magnus Ohman, Jack E. Smith, and Richard S. Stack

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BALANCED CARDIODYNAMICS... THE LINK TO ANTIANGINAL PROTECTION AND SAFETY



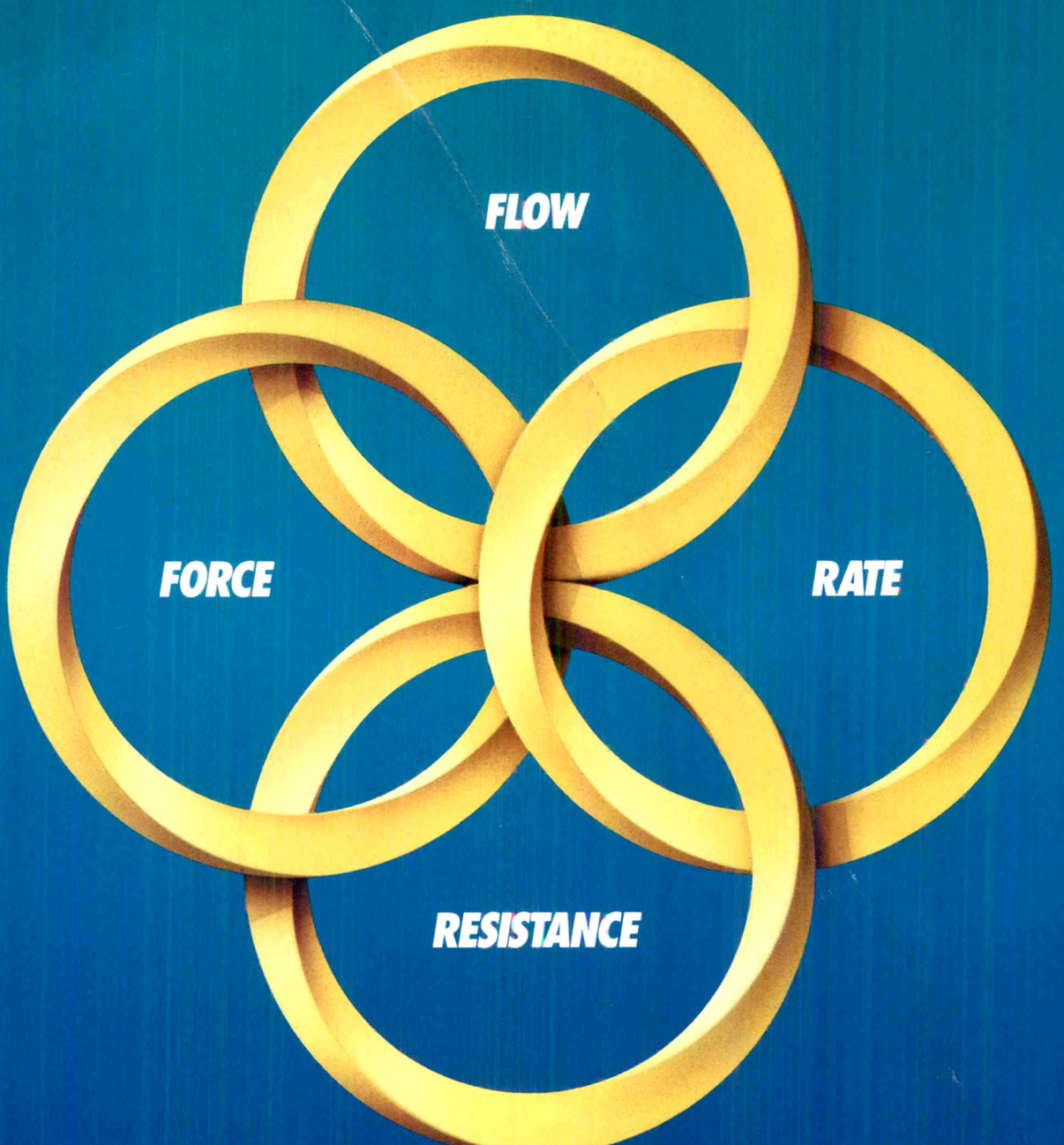
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* CARDIZEM (diltiazem HCl) is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

†Caution should be used in patients with CHF.

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—giving patients more pain-free days[10-12]*

RATE

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—without slowing patients down

RESISTANCE

Cardizem decreases peripheral resistance and myocardial work load[1-4]
—so patients can do more

FORCE

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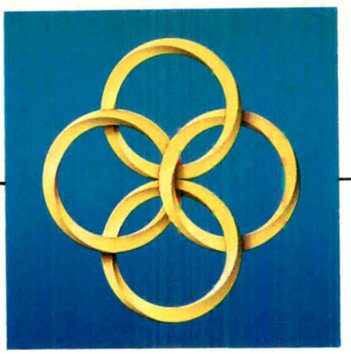
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Please see brief summary of prescribing information on next page.

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60 mg 90 mg 120 mg

BRIEF SUMMARY

CARDIZEM®
(diltiazem HCl) Tablets

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepctic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes, however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)

Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.



Usual maintenance dosage: 180 to 360 mg/day

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular: Angina, arrhythmia, AV block (first degree), AV block (second or third degree — see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope.

Nervous System: Amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase.

Dermatologic: Petechiae, pruritus, photosensitivity, urticaria.

Other: Amblyopia, CPK elevation, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

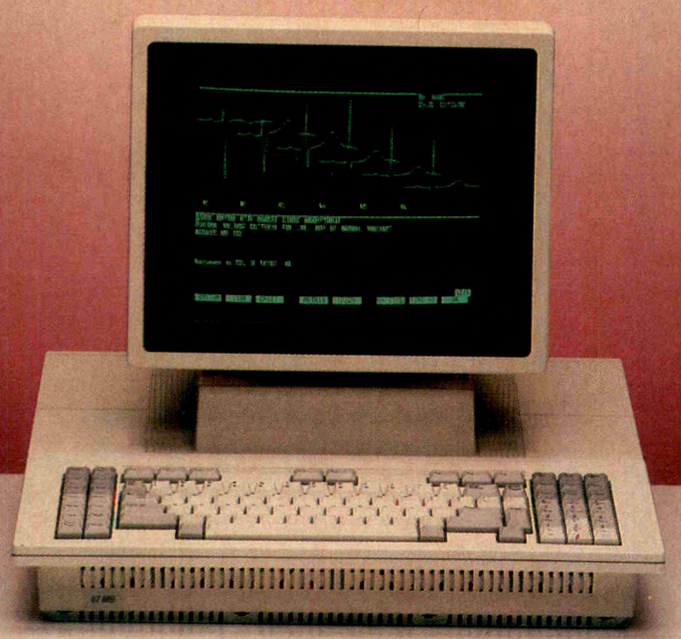
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The American Journal of Cardiology

OCTOBER 15, 1990, VOL. 66, NO. 12

CORONARY ARTERY DISEASE

897

Transient Left Ventricular Filling Abnormalities (Diastolic Stunning) After Acute Myocardial Infarction

Brian D. Williamson, Michael J. Lim, and Andrew J. Buda

To examine diastolic filling after acute myocardial infarction, Doppler echocardiograms were performed in 60 patients within 24 hours of infarction and again 7 days after infarction in a subgroup of 17. Fifteen patients with stable coronary artery disease served as control subjects. The infarct group had a lower total velocity time integral, velocity time integral E and velocity time integral 0.333 compared to the control group. In addition, velocity time integral A/total was significantly greater in the infarction group than the control group. The follow-up subgroup showed an increase in velocity time integral total, velocity time integral E and velocity time integral 0.333/total over the first 7 days after infarction. Patients with initial ejection fraction <40% or anterior infarction showed the greatest recovery during the 7-day period. Thus, left ventricular filling is further impaired during acute infarction, with the predominant impairment in early diastole. After infarction, filling parameters improve over the first 7 days after infarction, suggesting a recovery of diastolic stunning.

904

Comparison of Coronary and Myocardial Morphologic Findings in Patients With and Without Thrombolytic Therapy During Fatal First Acute Myocardial Infarction

S. David Gertz, Amy H. Kragel, Jay M. Kalan, Eugene Braunwald, William C. Roberts, and The TIMI Investigators

The hearts of 61 patients after a fatal first acute myocardial infarction (AMI) without percutaneous transluminal coronary angioplasty or coronary artery bypass grafting were studied. Comparison of 23 patients who received thrombolytic therapy 3 ± 1 hours after onset of symptoms with 38 patients who did not showed similar ages, gender, heart weight, frequency of hypertension, location of AMI, coronary narrowing and frequency of plaque rupture. Patients receiving tissue-plasminogen activator had a greater frequency of nonocclusive thrombi with a lower frequency of infarct-related arteries obstructed by thrombus at necropsy and a lower frequency of myocardial rupture. Plaque rupture was found to be responsible for total or near-total obstruction of the infarct-related artery in only 4 of 43 patients with plaque rupture (2 received thrombolytic therapy, 2 did not). The associated thrombus accounted for the total luminal obstruction

Continued on page A18



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10 Important Questions About Lipid-Lowering Therapy

Which Lipid-Lowering Agent...

1 Has been proven to improve mortality in a 15-year study of infarct survivors?

NIACIN Only niacin has been proven to significantly reduce mortality ($p = 0.004$). Mortality in men with ECG-demonstrated MI was 11% lower in the niacin group compared to the placebo group.[1]

2 Has been proven to significantly reduce the incidence of myocardial infarction recurrence?

NIACIN Niacin has been proven to reduce the incidence of definite nonfatal recurrent MI. In a 6-year prospective study the incidence of definite nonfatal MI was 10.4% for the niacin group (1,119 patients) and 14.7% for those receiving placebo.[1]

3 Reduces total cholesterol, LDL-cholesterol and triglycerides?

NIACIN and **LOVASTATIN** The bile acid sequestrants may raise triglycerides.[2] Gemfibrozil is effective in lowering triglycerides, but has variable effects on LDL-cholesterol. Lovastatin effectively lowers LDL and total cholesterol, but has only a modest effect on triglyceride levels. *Niacin reduces total cholesterol, LDL-cholesterol and triglycerides.*[1,2,3]

4 Is a drug of choice for LDL-cholesterol reduction in the NCEP (National Cholesterol Education Program, 1988) report?

NIACIN and **BILE ACID SEQUESTRANTS** These two agents were recommended by the NCEP as first-line therapy in reducing LDL-cholesterol.[2]

5 Is most effective in raising HDL-cholesterol (the most important lipid risk factor in coronary artery disease)?

NIACIN Niacin has the most marked effect in raising HDL-cholesterol. Increases in HDL-cholesterol are relatively modest with lovastatin. Gemfibrozil also increases HDL-cholesterol. The bile acid sequestrants are considered to be HDL-cholesterol neutral.[4]

6 Reduces progression of coronary artery disease when used with colestipol?

NIACIN and **LOVASTATIN** The CLAS trial demonstrated a significant reduction in lesion progression with the niacin/colestipol group.[5] In the FATS trial niacin/colestipol was compared to lovastatin/colestipol.[4] Both agents effectively halted the progression of atherosclerotic lesion. The best coronary angiography results were found in the niacin subgroup.

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7

Is the NCEP drug of choice in patients with high cholesterol and hypertriglyceridemia?

NIACIN Niacin was specified as the NCEP drug of choice in patients with both high cholesterol and high triglycerides. (Bile acid sequestrants may elevate triglycerides.)[2]

8

Can cost less than $100 per year?

NIACIN Approximate costs per year are reported in the literature as: niacin—$50 to $200; gemfibrozil—$600; lovastatin—$500 to $2,100[4] and cholestyramine—$500.[2]

9

Is well tolerated at effective doses by the majority of patients?

NIACIN, LOVASTATIN, GEMFIBROZIL, and CHOLESTYRAMINE Although lovastatin and gemfibrozil are better tolerated, most patients can be maintained at effective dose levels of all four agents.[2,3,4]

10

Is now recommended at lower doses?

NIACIN The latest studies show niacin is effective at low doses (<2 grams/day). Starting at 500 mg/day, or less, and titrating upward improves tolerance.[3,6]

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BRIEF SUMMARY: For full prescribing information, please see package insert.

INDICATIONS: Since no drug is innocuous, strict attention should be paid to the indications and contraindications, particularly when selecting drugs for long term use. Niacor® niacin tablets are indicated as adjunctive therapy in patients with significant hyperlipidemia (elevated cholesterol and/or triglycerides) who do not respond adequately to diet and weight loss.

Notice: It has not been established whether the drug-induced lowering of serum cholesterol or triglyceride levels has a beneficial effect, no effect, or a detrimental effect on the moribidity or mortality due to atherosclerosis including coronary heart disease. Investigations now in progress may yield an answer to this question.

CONTRAINDICATIONS: Niacor® niacin tablets, are contraindicated in patients with a known idiosyncrasy to niacin, with hepatic dysfunction, with active peptic ulcer or with arterial bleeding.

WARNINGS: Use of this drug in pregnancy, lactation or in women of child bearing age requires that the potential benefits of the drug be weighed against its possible hazards to the mother and child. Although fetal abnormalities have not been reported with this drug, its use as an antilipidemic agent requires high dosages, and animal reproduction or teratology studies have not been done. There are insufficient studies done for usage in children.

KEEP OUT OF REACH OF CHILDREN.

PRECAUTIONS: Great caution must be exercised when niacin is used in patients with coronary disease or gallbladder disease. Patients with a past history of jaundice, liver disease or peptic ulcer should be observed closely while taking the medication. Frequent monitoring of liver function tests and blood glucose should be performed during therapy to ascertain that the drug has no adverse effects on these organ systems. Antihypertensive drugs of the adrenergic-blocking type may have an additive vasodilating effect and produce postural hypotension. Elevated uric acid levels have occurred, therefore use with caution in patients predisposed to gout.

DRUG INTERACTIONS: Antihypertensive drugs may have an additive vasodilating effect and produce postural hypotension. Diabetic or potential diabetic patients should be observed closely in the event of decreased glucose tolerance. Adjustment of diet and/or hypoglycemic therapy may be necessary.

ADVERSE REACTIONS:

- Atrial fibrillation and other cardiac arrhythmias
- Decreased glucose tolerance
- Abnormalities of hepatic functional tests
- Gastrointestinal disorders
- Acanthosis Nigricans
- Hyperuricemia
- Hypotension
- Severe generalized flushing
- Activation of peptic ulcers
- Jaundice
- Dryness of the skin
- Pruritus
- Toxic amblyopia
- Transient headache

OVERDOSAGE: High doses of nicotinic acid may produce temporary flushing, pruritus, and gastrointestinal distress.

DOSAGE AND ADMINISTRATION: Usually Recommended Adult Dosage—1 to 2 grams three times a day. The dosage must be adjusted to the response of the patient. Start with two tablets (1 g) three times a day with food or after meals, taken with cold liquids, if necessary, to facilitate swallowing. Since low doses may control hyperlipidemia in some patients, the dosage should be individualized according to the effect on serum lipid levels. If the plasma cholesterol and/or triglyceride level does not show a decrease after a reasonable time at this dosage, an increase in dosage may be considered but requires careful titration and observation of the patient for unwanted effects. The dosage may be increased every 2 to 4 weeks, but in no case should the dosage exceed 6 grams a day.

Since flushing, pruritus and gastrointestinal distress appear frequently and tend to be dose-related, increase the dosage gradually in increments of 500mg (1 tablet) while carefully observing the patient and monitoring the plasma cholesterol and/or triglyceride level for therapeutic response and for adverse effects. Where the observed adverse reactions or potential hazards exceed the benefits of use, dosage should be reduced to the minimum recommended dosage and, where necessary, discontinued entirely.

HOW SUPPLIED: White scored tablets with "NIACOR" imprinted on one side, containing 500 mg niacin each, in bottles of 100. NDC#0245-0066-11. Dispense in tight container as defined in the USP. Store at controlled room temperature, 15°-30°C (59°-86°F).

CAUTION: Federal law prohibits dispensing without a prescription.

References

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Rev 0690 NDC 0245-0066-11

in the other patients with plaque rupture. Thus, thrombolytic therapy is still expected to be of value in most patients with plaque rupture and nonresistant thrombi.

910

Recombinant Tissue-Type Plasminogen Activator Followed by Heparin Compared with Heparin Alone for Refractory Unstable Angina Pectoris

Diego Ardissino, Paolo Barberis, Stefano De Servi, Antonio Mussini, Alberto Rolla, Luigi Visani, and Giuseppe Specchia

In a randomized, double-blind trial the short-term efficacy of treatment with recombinant tissue-type plasminogen activator (rt-PA) followed by heparin was assessed and compared with heparin treatment alone in 24 patients with unstable angina refractory to conventional medical treatment. Recurrences of ischemic attacks during a 72-hour follow-up period were documented in 9 of the patients given heparin alone, and in none of those given combined treatment. Kaplan-Meier curves analysis demonstrated a significantly higher probability of being ischemia free in the group of patients treated with rt-PA followed by heparin than in the group treated with heparin alone ($p < 0.01$). This study demonstrates that the addition of a thrombolytic agent to heparin may have a greater protective effect than heparin alone for the early management of recurrent anginal episodes in patients with unstable angina refractory to conventional medical treatment.

915

Role of Beta-Adrenergic Blockers After Percutaneous Transluminal Coronary Angioplasty

Sten R. Johansson, Carl Lamm, Göran Bondjers, Håkan Emanuelsson, and Åke Hjalmarson

Restenosis after percutaneous transluminal coronary angioplasty (PTCA) remains an unsolved problem. Different medical regimens have been largely unsuccessful. Experimental studies suggest a role for β blockers, but clinical studies are lacking. We evaluated 541 consecutive PTCA procedures where 86% of the patients were treated with β blockers (76% metoprolol, 34% others). The success and complication rates were not different with or without β blockers. Follow-up angiograms after 88% of the successful procedures revealed a total restenosis rate of 36%, not differing significantly with or without β blockers. This retrospective study indicates that treatment with β blockers after PTCA does not influence success or restenosis rates and can be continued if indicated from a antiischemic viewpoint.

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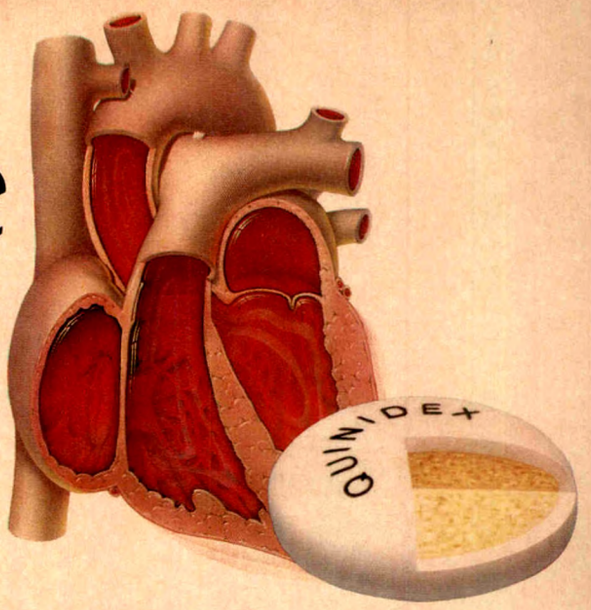
Functional Status After Coronary Artery Bypass Grafting and Percutaneous Transluminal Coronary Angioplasty

Jerilyn K. Allen, Sheila T. Fitzgerald, Robert T. Swank, and Diane M. Becker

A prospective study of 2 cohorts of patients of comparable age with similar preprocedure cardiac function who underwent either coronary artery by-

Continued on page A24

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Please see adjacent page for brief summary.

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The following is a brief summary only. Before prescribing, see complete prescribing information in Quinidex product labeling.

Contraindications: Intraventricular conduction defects. Complete A-V block. A-V conduction disorders caused by digitalis intoxication. Aberrant impulses and abnormal rhythms due to escape mechanisms. Idiosyncrasy or hypersensitivity to quinidine or related cinchona derivatives. Myasthenia gravis.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio, resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.

Reports in the literature indicate that serum concentrations of digoxin may increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored for digitalis toxicity. Reduction of digoxin dosage may have to be considered.

Manifestations of quinidine cardiotoxicity such as excessive prolongation of the QT interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.

In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function manifested by hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.

Quinidine should be used with extreme caution in patients with incomplete AV block since complete AV block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication.

Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in serum, leading to toxicity.

Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or serum levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.

Cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4–8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.

Precautions: *General*—All the precautions applying to regular quinidine therapy apply to this product. Hypersensitivity or anaphylactoid reactions to quinidine, although rare, should be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and determination of serum quinidine levels are indicated when large doses of quinidine are used or with patients who present an increased risk.

Information for Patients—As with all solid dosage medications, Quinidex Extentabs should be taken with an adequate amount of fluid, preferably with the patient in an upright position to facilitate swallowing. They should be swallowed whole in order to preserve the controlled-release mechanism.

Laboratory Tests—Periodic blood counts and liver and kidney function tests should be performed during long-term therapy; the drug should be discontinued if blood dyscrasias or evidence of hepatic or renal dysfunction occurs.

Drug Interactions

Drug	Effect
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased serum concentration of digoxin (See Warnings)
Quinidine with amiodarone	Increased serum concentration of quinidine
Quinidine with cimetidine	Prolonged quinidine half-life and an increase in serum quinidine level
Quinidine with ranitidine	Premature ventricular contractions and/or bigeminy
Quinidine with verapamil	Increased quinidine half-life and an increase in serum quinidine level; potential hypotensive reactions
Quinidine with nifedipine	Decreased serum concentrations of quinidine

Carcinogenesis: Studies in animals have not been performed to evaluate the carcinogenic potential of quinidine.

Pregnancy, Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinidex Extentabs should be administered to a pregnant woman only if clearly indicated.

Nonteratogenic Effects: Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Labor and Delivery—There is no known use for Quinidex Extentabs in labor and delivery. However, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Nursing Mothers—Because of passage of the drug into breast milk, caution should be exercised when Quinidex Extentabs are administered to a nursing woman.

Pediatric Use—There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinidex Extentabs in children.

Adverse Reactions: Symptoms of cinchonism, such as ringing in the ears, loss of hearing, dizziness, lightheadedness, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal.

Gastrointestinal—Nausea, vomiting, abdominal pain, diarrhea, anorexia, granulomatous hepatitis (which may be preceded by fever), esophagitis.

Cardiovascular—Ventricular extrasystoles occurring at a rate of one or more every 6 normal beats; widening of the QRS complex and prolonged QT interval; complete A-V block; ventricular tachycardia and fibrillation; ventricular flutter; torsade de pointes; arterial embolism; hypotension; syncope.

Central Nervous System—Headache, vertigo, apprehension, excitement, confusion, delirium, dementia, ataxia, depression.

Ophthalmologic and Otologic—Disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata), optic neuritis, reduced visual field.

Dermatologic—Cutaneous flushing with intense pruritus, photosensitivity, urticaria, rash, eczema, exfoliative eruptions, psoriasis, abnormalities of pigmentation.

Hypersensitivity—Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatotoxicity, granulomatous hepatitis (See Warnings), purpura, vasculitis.

Hematologic—Thrombocytopenia, thrombocytopenic purpura, agranulocytosis, acute hemolytic anemia, hypoprothrombinemia, leukocytosis, shift to left in WBC differential, neutropenia.

Immunologic—Systemic lupus erythematosus, lupus nephritis.

Miscellaneous—Fever, increase in serum skeletal muscle creatine phosphokinase, arthralgia, myalgia.

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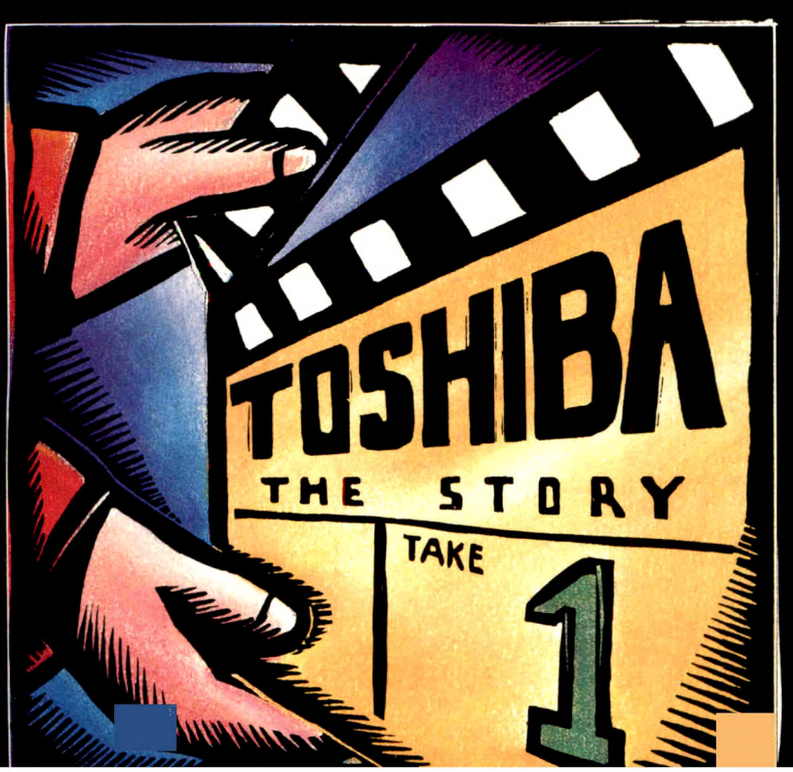
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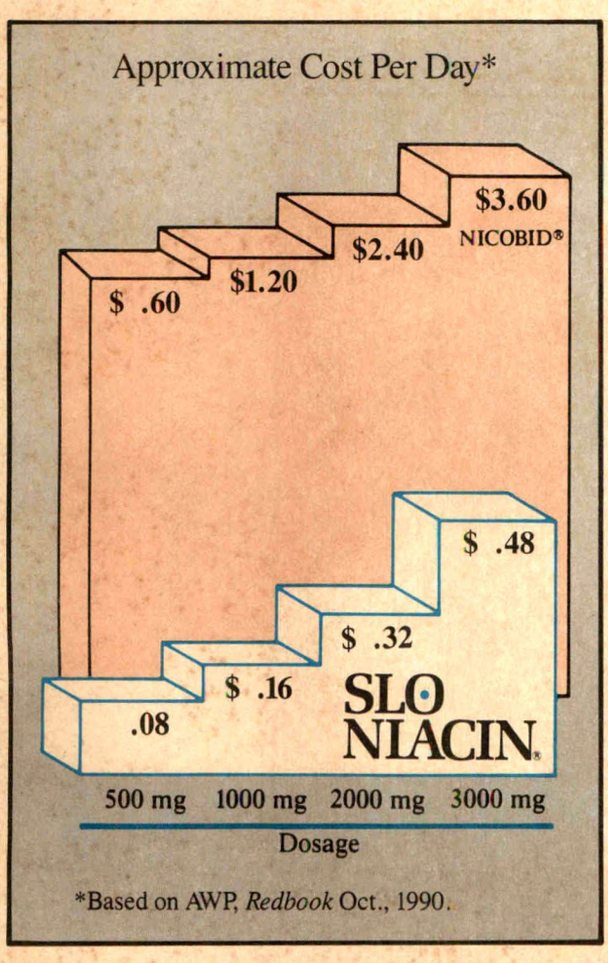


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C. J. Lavie, et al.: *Postgraduate Medicine*, May 15, 1990.

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pass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA) was carried out to examine functional status outcomes during the first year of recovery. Within the CABG group, significant improvements in all dimensions of functional status were noted over the year. Patients undergoing PTCA demonstrated significant improvement in all dimensions except for the quality of social interaction. When the 2 groups were compared, the PTCA group demonstrated greater participation in routine daily physical and social activities for the first 6 months, but the apparent advantage disappeared at 1 year. Measures of psychological and work functioning indicated better functioning after CABG than after PTCA.

926

Patient-Related Variables and Restenosis After Percutaneous Transluminal Coronary Angioplasty—A Report from the M-HEART Group

Robert G. Macdonald, Mark A. Henderson, John W. Hirshfeld, Jr., Sheldon H. Goldberg, Theodore Bass, George Vetrovec, Michael Cowley, Andrew Taussig, Hall Whitworth, James R. Margolis, James A. Hill, Ralph Jugo, and Carl J. Pepine for the M-HEART Group

As part of a multicenter restenosis trial (M-HEART) we prospectively collected data to determine whether there is an association between patient-related variables and risk of restenosis after coronary angioplasty. Variables analyzed were age, sex, history of previous myocardial infarction, smoking, diabetes, severity and duration of angina. An angiographic restudy was performed in 510 patients (71%), providing 598 dilated lesions for analysis. None of the variables analyzed had a statistically significant association with restenosis.

932

Results of Percutaneous Transluminal Coronary Angioplasty of High-Risk Angulated Stenoses

Stephen G. Ellis and Eric J. Topol

To better characterize the factors associated with the heightened procedural risk of coronary angioplasty (PTCA) of angulated stenoses and to identify means of lessening that risk, 100 sequentially treated patients undergoing PTCA of stenoses located at ≥45° bends were characterized for 27 clinical, anatomic and procedural variables, and the clinical outcome of angioplasty was related to these variables. Procedural success was achieved in only 70% of patients with angulated stenoses, compared with 306 of 344 (89%) contemporary procedures involving nonangulated stenoses, and major ischemic complications (death, bypass surgery or myocardial infarction) occurred in 13% of patients with angulated stenoses compared with 12 of 344 (3.5%) with nonangulated stenoses (both $p < 0.001$). The presence of associated thrombus, stenosis length ≥10 mm or age ≥65 years led to an even higher risk of major complications (9 of 44, 20.5%), while highly experienced angioplasty operators and the use of polyethylene terephthalate balloons appeared to decrease risk and increase the likelihood of success. PTCA of such stenoses should be undertaken only cautiously and in carefully selected patients.

Continued on page A30

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INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, cardiogenic shock, heart block greater than first degree, and bronchial asthma.
Please see adjacent page for brief summary of prescribing information.

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*

INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. INDERAL LA is formulated to provide a sustained release of propranolol hydrochloride. INDERAL LA is available as 60 mg, 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective, beta-adrenergic receptor-blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor-stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (60, 80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL Tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg-for-mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure, and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first-degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned, the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (eg, chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, eg, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta blockers should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. Following insulin-induced hypoglycemia, propranolol may cause a delay in the recovery of blood glucose to normal levels.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol may change thyroid function tests, increasing T_4 and reverse T_3, and decreasing T_3.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case, this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. GENERAL: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL (propranolol HCl) is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

CLINICAL LABORATORY TESTS: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL (propranolol HCl) is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Caution should be exercised when patients receiving a beta blocker are administered a calcium-channel-blocking drug, especially intravenous verapamil, for both agents may depress myocardial contractility or atrioventricular conduction. On rare occasions, the concomitant intravenous use of a beta blocker and verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure, or recent myocardial infarction.

Aluminum hydroxide gel greatly reduces intestinal absorption of propranolol.

Ethanol slows the rate of absorption of propranolol.

Phenytoin, phenobarbitone, and *rifampin* accelerate propranolol clearance.

Chlorpromazine, when used concomitantly with propranolol, results in increased plasma levels of both drugs.

Antipyrine and *lidocaine* have reduced clearance when used concomitantly with propranolol.

Thyroxine may result in a lower than expected T_3 concentration when used concomitantly with propranolol.

Cimetidine decreases the hepatic metabolism of propranolol, delaying elimination and increasing blood levels.

Theophylline clearance is reduced when used concomitantly with propranolol.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

PREGNANCY: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: Bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Light-headedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate formulations, fatigue, lethargy, and vivid dreams appear dose related.

Gastrointestinal: Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: Pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: Bronchospasm.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: Alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL Tablets to INDERAL LA Capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg-for-mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary, especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three- to seven-day intervals until optimal response is obtained. Although individual patients may respond at any dosage level, the average optimal dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

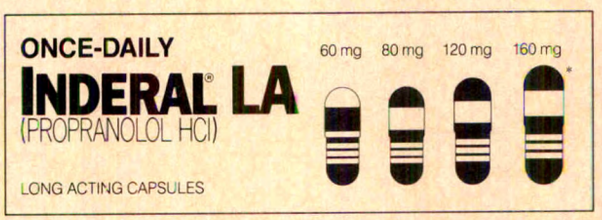
If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimal migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximal dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

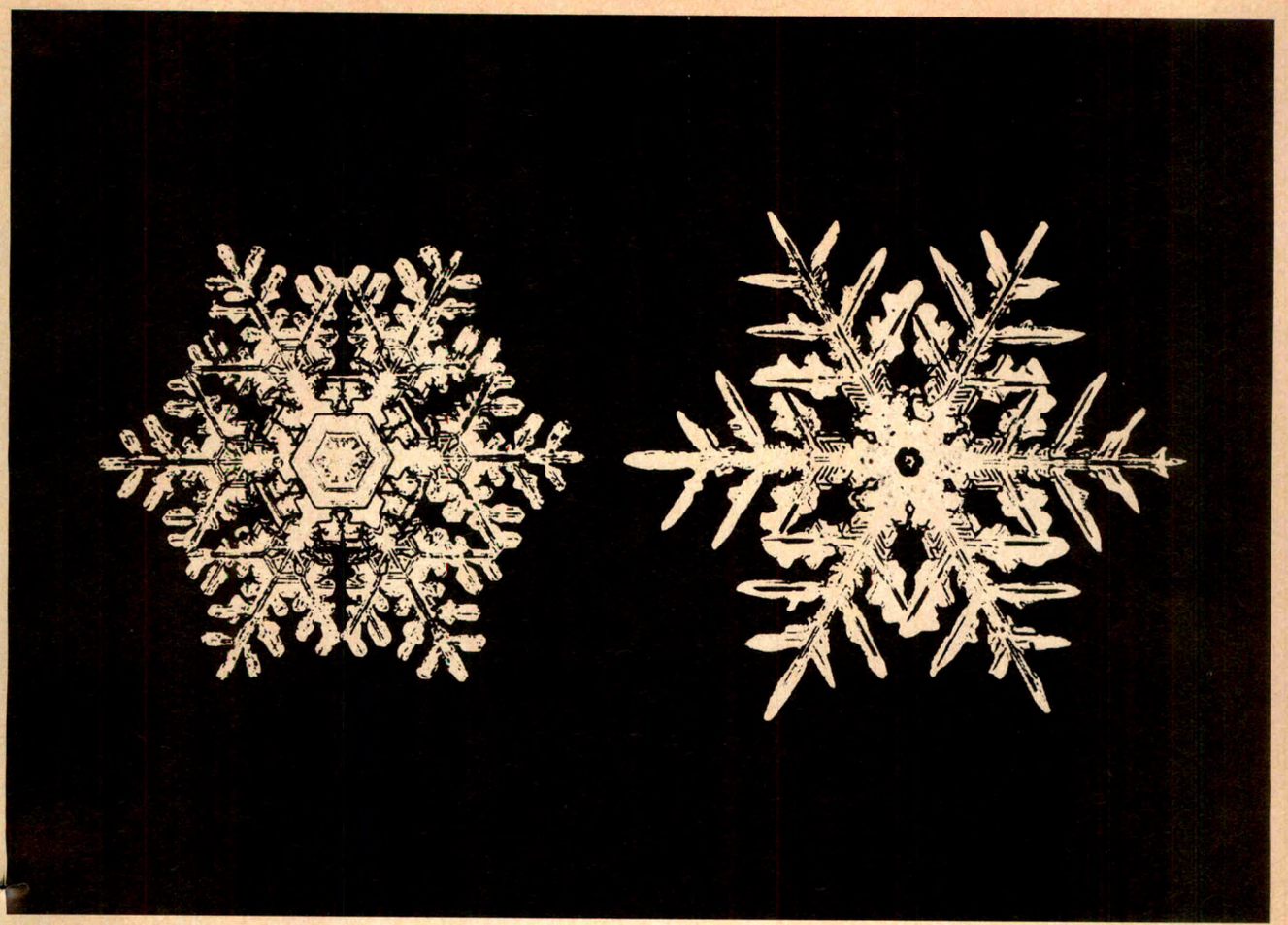
*The appearance of these capsules is a registered trademark of Wyeth-Ayerst Laboratories.



WYETH-AYERST LABORATORIES
Philadelphia, PA 19101

52418

© 1988, Wyeth-Ayerst Laboratories.



No two are exactly alike.

Because body chemistry differs from person to person, we often need a choice of drugs to treat the same illness.

You've heard it said that no two snowflakes are exactly alike. The variety is endless. Much the same is true of the human body.

Take the case of two patients suffering from hypertension. Both under the care of the same physician, who prescribes the same medication for each. One patient responds to the medication while the other reports unpleasant side-effects. Thanks to the diversity of drugs available to treat this illness, the doctor is able to prescribe another medicine that works without the side effects.

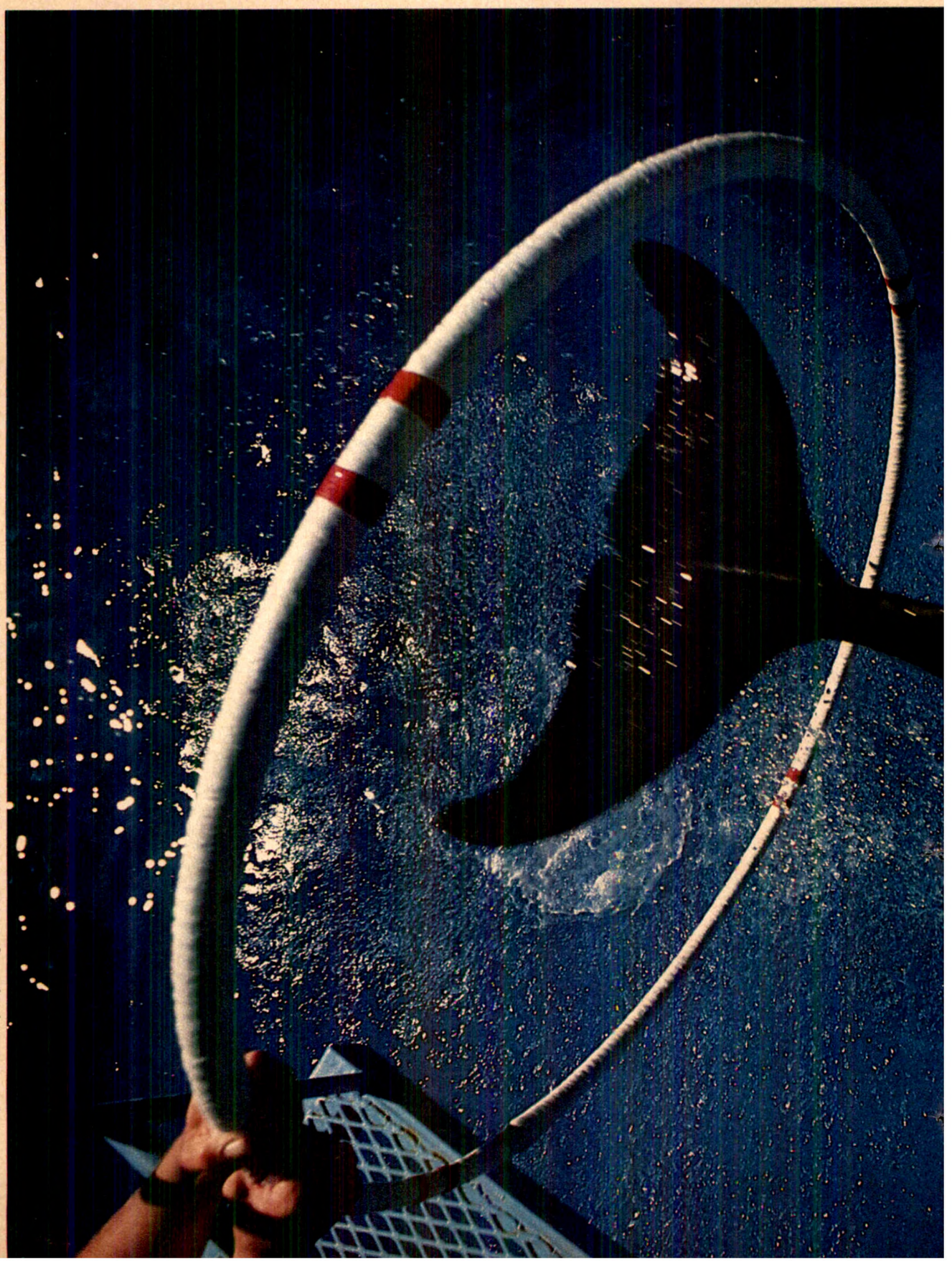
To maintain the high standards of quality care, and because some drugs work better than others on different people, it is essential to have this diversity.

America's research-based pharmaceutical companies are committed to providing a wide range of drugs of the highest quality to serve the public. Why? Because the public is made up of different people requiring different treatment—even when they suffer from the same illness.

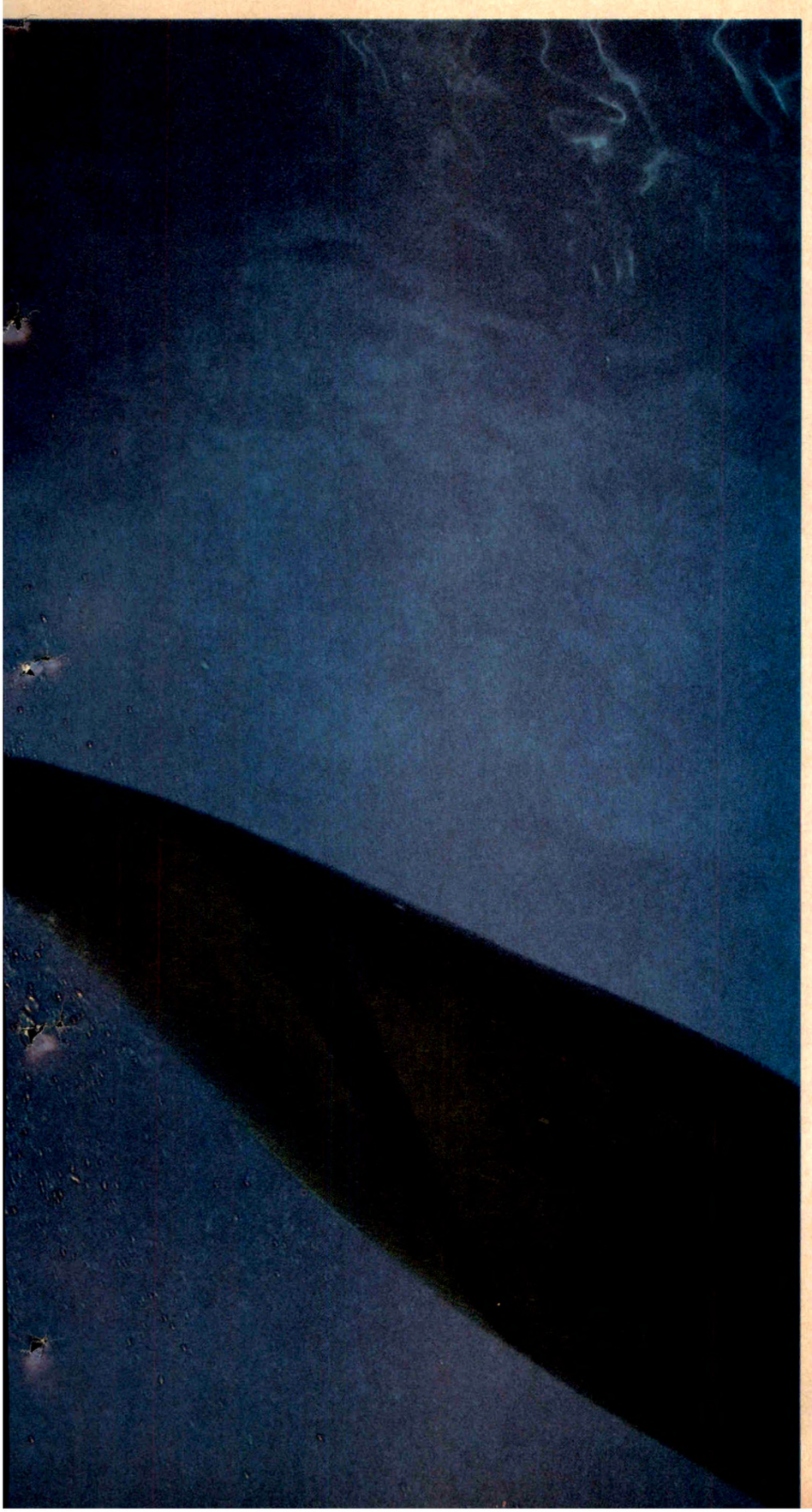
Pharmaceutical Manufacturers Association

IF A NEW MEDICINE CAN HELP, WE'RE WORKING ON IT.

When it comes to customer support, we'll do the same for you.



*Based on independent surveys by Datapro and IMS America. © 1990 Hewlett-Packard MG03008



Jump through hoops. Bend over backwards. Go the distance. At Hewlett-Packard, we'll do what it takes to help you do your job better.

You'll find that we've designed HP ACCOMPLISH Customer Support to help clinicians use technology more effectively in order to deliver quality patient care.

How? Through customized education programs, fast telephone consultation and top quality on-site assistance.

HP ACCOMPLISH Customer Support

- *Local and worldwide resources*
- *On-site services*
- *Clinical and biomedical education*
- *Dedicated response centers*
- *Consultation and customization*

So it should come as no surprise that we've been getting top marks for customer support for years.*

HP ACCOMPLISH Customer Support. Because it's easier to get things done when you've got someone jumping through hoops for you.

There is a better way.

HEWLETT PACKARD

938
Quantitative Angiographic Comparison of the Immediate Success of Coronary Angioplasty, Coronary Atherectomy and Endoluminal Stenting
David W. M. Muller, Stephen G. Ellis, Darrell L. Debowey, and Eric J. Topol

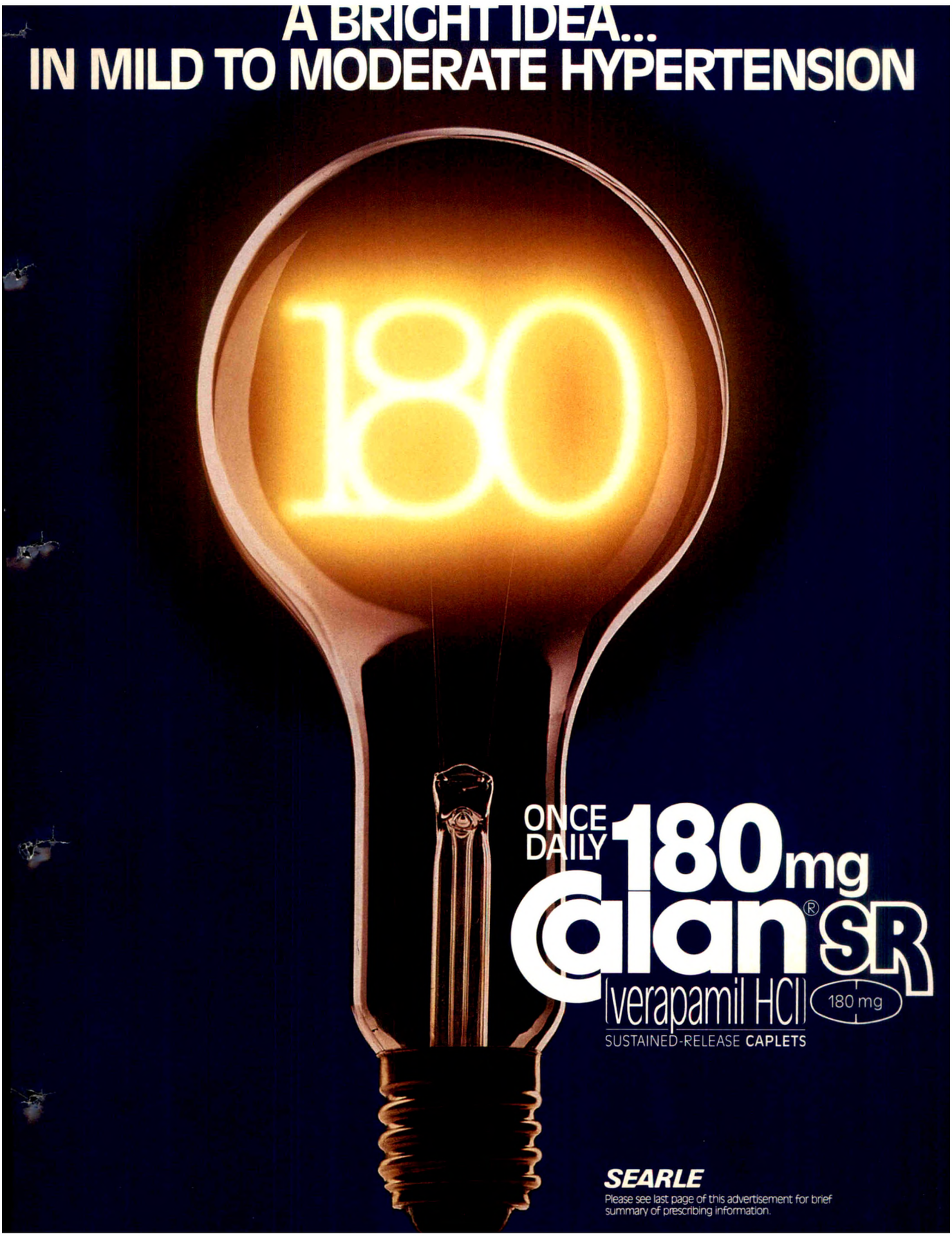
Pre- and postprocedural coronary angiograms were quantitatively evaluated in 18 patients undergoing coronary atherectomy, in 21 patients treated by endoluminal coronary stenting and in 39 matched patients undergoing coronary balloon angioplasty. The computer-matched variables included patient age and sex, and lesion site and severity. Lesion complexity was matched visually. Where possible, coronary stenoses were also matched according to whether they were de novo or restenosis lesions. The reduction in coronary stenosis severity was significantly greater after either coronary atherectomy or stenting than after balloon angioplasty. The superior results with these 2 devices were achieved with a lower incidence of moderate or severe medial dissection. These findings suggest that, in selected patients, coronary atherectomy or stenting may be preferable to conventional balloon angioplasty.

943
Early Postoperative Balloon Coronary Angioplasty for Failed Coronary Artery Bypass Grafting
Joel K. Kahn, Barry D. Rutherford, David R. McConahay, Lee V. Giorgi, Warren L. Johnson, Thomas M. Shimshak, and Geoffrey O. Hartzler

To examine the usefulness of coronary angioplasty for the treatment of recurrent ischemia early after coronary artery bypass grafting (CABG), 45 patients were treated from 2 to 90 days after CABG. The major anatomic mechanism of recurrent ischemia was complete vein graft occlusion in 12 patients (27%), internal mammary artery occlusion in 3 (7%), vein graft stenoses in 13 (29%), internal mammary artery stenoses in 10 (22%), unbypassed disease in 4 (8%) and disease distal to the graft insertion site in 3 (7%). Angioplasty was successful at 91 of 98 sites (93%). There were 2 in-hospital deaths and 2 myocardial infarctions. Two additional patients underwent repeat CABG before discharge after uncomplicated but failed angioplasty. At late follow-up of the 43 survivors (mean 44 months), there were 4 deaths, 2 of which were noncardiac. Repeat CABG was required in only 3 patients and repeat angioplasty was performed in 10. Thus, percutaneous transluminal coronary angioplasty can relieve myocardial ischemia after failed CABG in the majority of patients.

Continued on page A35

A BRIGHT IDEA...
IN MILD TO MODERATE HYPERTENSION



ONCE DAILY **180 mg**

Calan® SR

(verapamil HCl) 180 mg

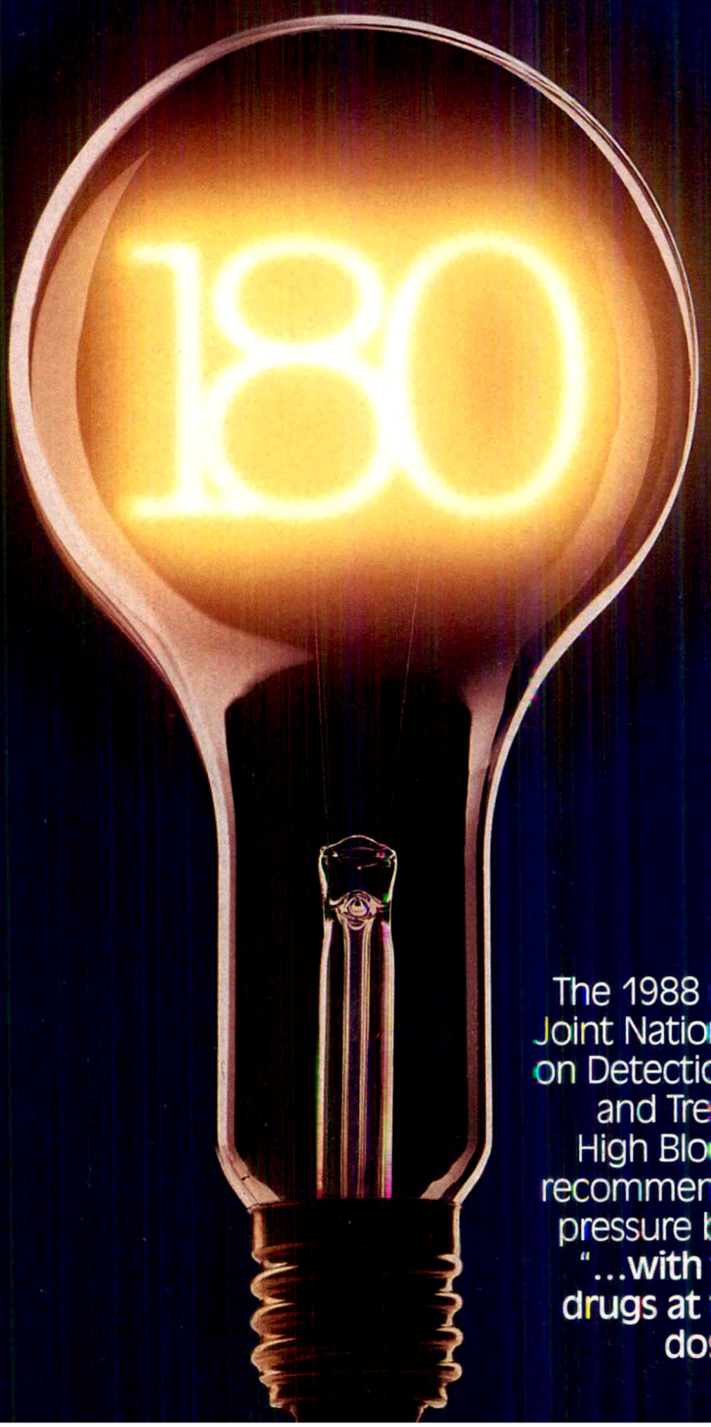
SUSTAINED-RELEASE **CAPLETS**

SEARLE

Please see last page of this advertisement for brief summary of prescribing information.

ONCE-A-DAY, SINGLE-AGENT THERAPY CONSISTENT WITH 1988 JNC RECOMMENDATION...

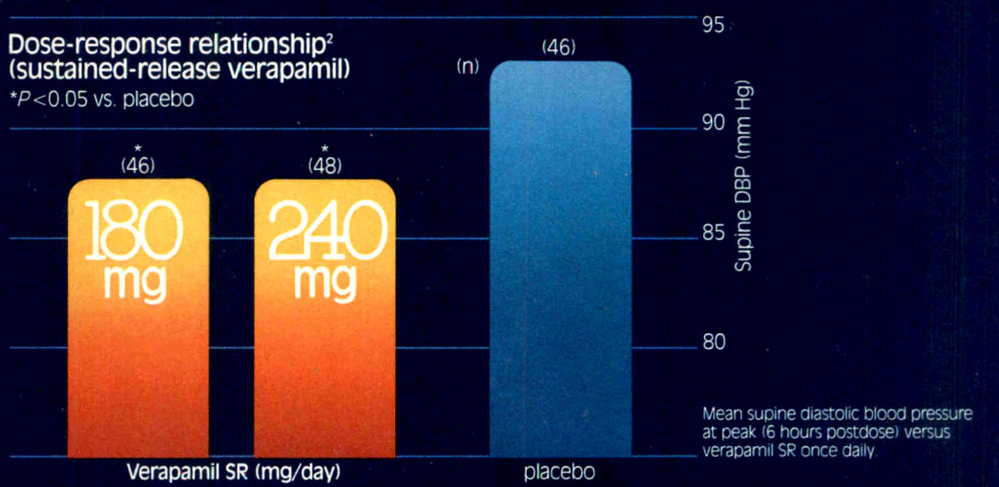
180-mg CALAN SR
(verapamil HCl)



The 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure recommends that blood pressure be controlled "**...with the fewest drugs at their lowest dose....**"[1]

HIGH SINGLE-AGENT EFFICACY...

180 mg--EFFICACY DEMONSTRATED COMPARABLE TO 240 mg[2]



Mean supine diastolic blood pressure at peak (6 hours postdose) versus verapamil SR once daily.

180 mg...

— 24-HOUR CONTROL WITH ONCE-DAILY DOSING[2†]
— LOW-DOSE, WELL-TOLERATED[‡] THERAPY[2]
A MORE ECONOMICAL CHOICE[§]

When you want high single-agent efficacy in a lower dose, prescribe...

ONCE DAILY **180 mg**

Calan® SR

verapamil HCl 180 mg

SUSTAINED-RELEASE **CAPLETS**

A BRIGHT IDEA IN VERAPAMIL SR THERAPY

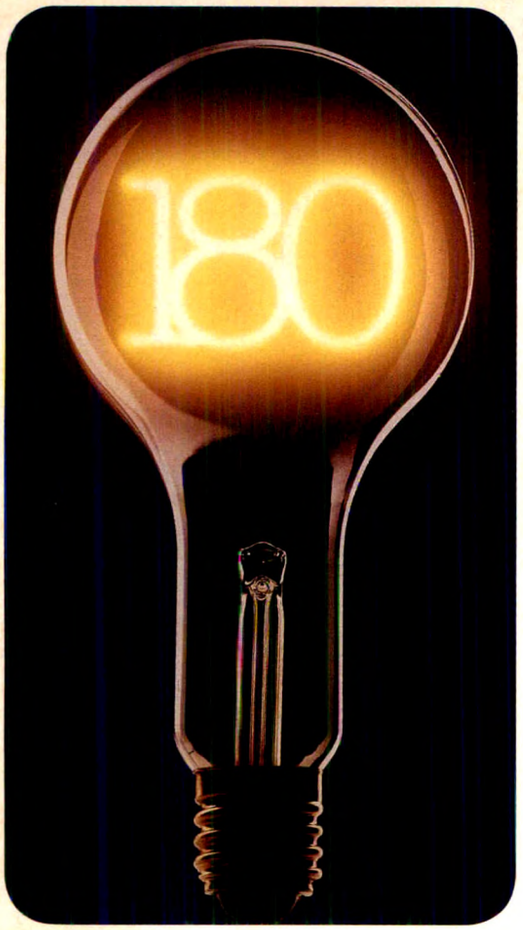
†Total daily dosages above 240 mg should be administered in divided doses. Calan SR should be administered with food.

‡Constipation, which is easily managed in most patients, is the most commonly reported side effect of Calan SR.

§Price comparison versus 240-mg Calan SR.

Please see last page of this advertisement for references and a brief summary of prescribing information.

SEARLE



A BRIGHT IDEA FOR HYPERTENSIVE PATIENTS

LIPID NEUTRAL[3]

-Not associated with alterations in total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides

LOW INCIDENCE OF VASODILATORY SIDE EFFECTS[4]*

When you want high single-agent efficacy in a lower dose, prescribe...

ONCE DAILY **180mg**

Calan® SR

Verapamil HCl 180 mg

SUSTAINED-RELEASE **CAPLETS**

*Constipation, which is easily managed in most patients, is the most commonly reported side effect of Calan SR.

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, increased urination, spotty menstruation, impotence.

12/21/89 • P90-W198V

References: **1.** 1988 Joint National Committee: The 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1988;148:1023-1038. **2.** Data on file, G.D. Searle & Co. **3.** Krone W, Nägele H: Effects of antihypertensives on plasma lipids and lipoprotein metabolism. *Am Heart J* 1988;116:1729-1734. **4.** Calan SR complete prescribing information.

Address medical inquiries to:
G.D. Searle & Co.
Medical & Scientific Information Department
4901 Searle Parkway
Skokie, IL 60077

SEARLE *G.D. Searle & Co.*
Box 5110, Chicago, IL 60680

A90CA4514T

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

947
Electrophysiologic and Electrocardiographic Effects, Efficacy and Safety of Encainide in Malignant Ventricular Arrhythmias Associated with Coronary Artery Disease

Andrew R. Weintraub, Antonis S. Manolis, and N.A. Mark Estes III

The electrophysiologic and electrocardiographic effects, efficacy and safety of encainide were evaluated in 48 patients with coronary artery disease undergoing programmed stimulation for ventricular tachyarrhythmias. To evaluate the efficacy of encainide by programmed stimulation, 48 patients with coronary artery disease and inducible ventricular tachycardia (VT) (nonsustained in 8 and sustained in 35) or fibrillation (5) received oral encainide (mean daily dosage 80 ± 11 mg). Left ventricular ejection fraction averaged 34 ± 13%. Patients had failed a mean of 2.2 ± 1.1 drugs before encainide. Encainide was discontinued before follow-up electrophysiologic testing in 5 patients because of spontaneous development of new sustained VT. Overall, encainide's efficacy in preventing VT induction by programmed stimulation was 10% (5 of 48), while its proarrhythmic effect (early and during electrophysiologic testing) was 31% (15 of 48). Of the 5 patients without inducible VT who were placed on long-term encainide therapy, 1 returned within 4 weeks of hospital discharge with VT recurrence. Encainide has limited efficacy (10%) for prevention of ventricular arrhythmia induction by programmed stimulation and a high incidence of proarrhythmia (31%).

954
Role of Alcohol in Recurrences of Atrial Fibrillation in Persons <65 Years of Age

Pekka Koskinen, Markku Kupari, and Hannu Leinonen

We examined the etiologic role of alcohol in recurrences of atrial fibrillation (AF) in 98 consecutive patients <65 years of age. Compared to 98 age- and sex-matched hospital control subjects, the AF patients had consumed significantly more alcohol during the week preceding the arrhythmia. Multivariate analysis of data on AF patients and 50 randomly selected out-of-hospital control subjects showed that alcohol intake and a positive response to 1 or more of the CAGE questions (a screening test for alcohol abuse) were related, independently of serum potassium, associated disease and stress or lack of sleep, to AF in men.

959
Circadian Rhythmicity of Rate-Normalized QT Interval in Hypothyroidism and Its Significance for Development of Class III Antiarrhythmic Agents

Jonnalagedda S. M. Sarma, Kalyanasundaram Venkataraman, Pascal Nicod, Ralf Polikar, Johana Smith, Mary P. Schoenbaum, and Bramah N. Singh

Lengthening of repolarization and refractoriness occurs in hypothyroidism; it is associated with a reduced probability of arrhythmias. Using a new computer-assisted technique to measure QT interval, we analyzed 24-hour Holter tapes before and after (8 to 12 weeks) thyroxine (T_4) replace-

ment in 10 patients with hypothyroidism; the findings were compared to those in 6 normal control subjects. QTc interval was prolonged ($p < 0.02$) and heart rate decreased ($p < 0.005$) during the hypothyroid state. Circadian variation in QTc and heart rate was statistically significant in all groups studied ($p < 0.001$), but the circadian rhythmicity of QTc interval and heart rate were out of phase; the maximum prolongation of QTc occurred between midnight and 6 A.M. The QTc interval remained significantly prolonged after 8 to 12 weeks of T_4 replacement, when biochemical indexes of hypothyroidism had returned to normal values. Our data have significant implications for the development of new class III antiarrhythmic agents.

964

Chronic Transvenous Pacemaker Lead Removal Using a Unique, Sequential Transvenous System

George K. Brodell, Lon W. Castle, James D. Maloney, and Bruce L. Wilkoff

Transvenous removal of 43 consecutive chronic pacemaker leads was successful in 28 patients. A unique locking stylet and telescoping sheaths are used to provide consistent results. Chronic pacemaker leads can be reliably removed without thoracotomy. Both a unique locking stylet to allow traction without lead elongation and a sheath to dilate and detach adherent fibrous tissue are needed for consistent success. Recognized complications included myocardial avulsion without sequelae, subacute hemothorax, subclavian vein thrombosis and transient hypotension.

SYSTEMIC HYPERTENSION

967

Comparison of the Antihypertensive Efficiency of Nitrendipine, Metoprolol, Mepindolol and Enalapril Using Ambulatory 24-Hour Blood Pressure Monitoring

Joachim Schrader, Gerhard Schoel, Heike Buhr-Schinner, Michael Kandt, Gerhard Warneke, Victor W. Armstrong, and Fritz Scheler

In a randomized 6-month study on 201 patients, the antihypertensive efficiency of nitrendipine, metoprolol, mepindolol and enalapril was compared as monitored by 24-hour ambulatory blood pressure measurements. Normotension as assessed by casual blood pressure measurements was observed in all 4 groups after 6 months of treatment without significant differences between the groups. Despite comparable casual blood pressure control, the groups differed significantly in their mean 24-hour measurements. The greatest systolic and diastolic blood pressure decreases were seen in the metoprolol group. Metoprolol was also the most effective drug in decreasing the frequency of systolic pressure peaks >180 mm Hg. Both β blockers and enalapril significantly decreased the morning blood pressure increase compared to the values before treatment, while nitrendipine did not.

Continued on page A40

SQUIBB

ADD CAPOTEN EARLY

Whether or not your heart failure patients are receiving digitalis*...



IN MILD, MODERATE, AND SEVERE HEART FAILURE

(NYHA Class II, III, and IV)

CAPOTEN®

(captopril tablets)

CLOSING THE LOOP IN HEART FAILURE THERAPY

*CAPOTEN is indicated in patients with heart failure who have not responded adequately to treatment with diuretics and digitalis. Although the beneficial effect of captopril in heart failure does not require the presence of digitalis, most controlled clinical trial experience with captopril has been in patients receiving digitalis as well as diuretic treatment. Consequently, CAPOTEN should generally be added to both of these agents except when digitalis use is poorly tolerated or otherwise not feasible. In using CAPOTEN, consideration should be given to the risk of neutropenia/agranulocytosis. Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white blood cells or immune response. Evaluation of heart failure patients should always include assessment of renal function. See INDICATIONS, CONTRAINDICATIONS, WARNINGS, and ADVERSE REACTIONS in the brief summary on adjacent page.

CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension—CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/ agranulocytosis (see WARNINGS). CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in the treatment of congestive heart failure in patients who have not responded adequately to treatment with diuretics and digitalis. CAPOTEN should generally be added to both of these agents except when digitalis use is poorly tolerated or otherwise not feasible.

CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product.

WARNINGS: Angioedema—Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been seen in patients treated with ACE inhibitors, including captopril. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Emergency therapy, including but not necessarily limited to, subcutaneous administration of a 1:1000 solution of epinephrine should be promptly instituted.

Neutropenia/Agranulocytosis—Neutropenia (<1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins >1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses >150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]). In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function*—Hypertension—Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure—About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis*—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia*—If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension—Patients on Diuretic Therapy*—Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity—In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis—Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Lithium—Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C: Embryocidal effects and craniofacial malformations were observed in rabbits. *Human Experience*—There are no adequate and well-controlled studies of captopril in pregnant women. Data are available that show captopril crosses the human placenta. Captopril should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Based on post-marketing experience with all ACE inhibitors, the following information has been collected. Inadvertent exposure limited to the first *trimester* of pregnancy does not appear to affect fetal outcome adversely. Fetal exposure during the second and third trimester of pregnancy has been associated with fetal and neonatal morbidity and mortality.

When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported. Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate. Problems associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors but it is not clear whether they are related to ACE inhibition, maternal hypertension or the underlying prematurity.

There is no experience with exchange transfusion, hemodialysis or peritoneal dialysis for removing captopril from the neonatal circulation.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal—About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic—Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic—Rash, (usually maculopapular, rarely urticarial), often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular—Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia—Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months).

Angioedema—Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been reported in approximately one in 1000 patients. Angioedema involving the upper airways has caused fatal airway obstruction. (See WARNINGS.)

The following have been reported in about 0.5 to 2 percent of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials: gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias.

Other clinical adverse effects reported since the drug was marketed are listed below by body system. In this setting, an incidence or causal relationship cannot be accurately determined.

General: Asthenia, gynecomastia.
Cardiovascular: Cardiac arrest, cerebrovascular accident, syncope.
Dermatologic: Bullous pemphigus.
Gastrointestinal: Pancreatitis, glossitis.
Hematologic: Anemia, including aplastic and hemolytic.
Hepatobiliary: Hepatitis, including rare cases of necrosis, cholestasis.
Metabolic: Symptomatic hyponatremia.
Musculoskeletal: Myalgia, myasthenia.
Nervous/Psychiatric: Ataxia, confusion, depression, nervousness, somnolence.
Respiratory: Bronchospasm, eosinophilic pneumonitis, rhinitis.
Special Senses: Blurred vision.
Urogenital: Impotence.

As with other ACE inhibitors, a syndrome has been reported which includes: fever, myalgia, arthralgia, rash or other dermatologic manifestations, eosinophilia and an elevated ESR. Findings have usually resolved with discontinuation of treatment.

Altered Laboratory Findings: *Serum Electrolytes: Hyperkalemia:* small increases in serum potassium, especially in patients with renal impairment (see PRECAUTIONS).

Hyponatremia: particularly in patients receiving a low sodium diet or concomitant diuretics.

BUN/Serum Creatinine: Transient elevations of BUN or serum creatinine especially in volume or salt depleted patients or those with renovascular hypertension may occur. Rapid reduction of longstanding or markedly elevated blood pressure can result in decreases in the glomerular filtration rate and, in turn, lead to increases in BUN or serum creatinine.

Hematologic: A positive ANA has been reported.

Liver Function Tests: Elevations of liver transaminases, alkaline phosphatase, and serum bilirubin have occurred.

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, and 50 mg in bottles of 100 and 1000; 100 mg in bottles of 100; and in UNIMATIC® unit-dose packs of 100 tablets. (J3-658R)

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Issued: February 1990

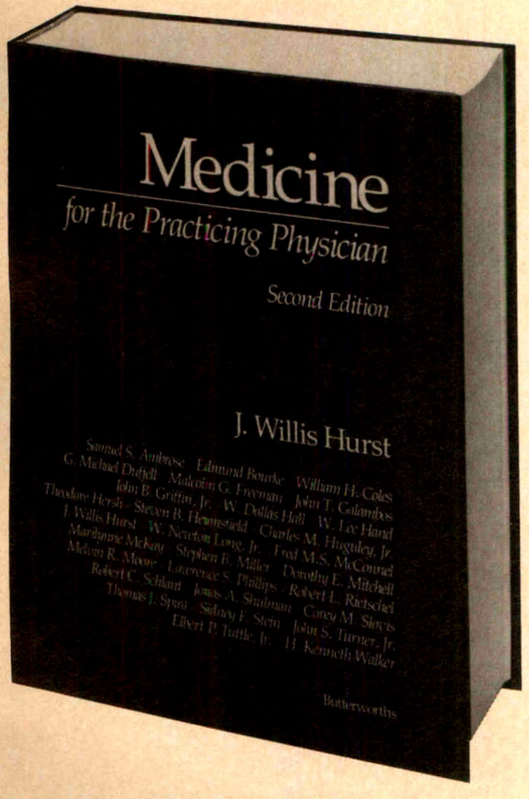
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CONGESTIVE HEART FAILURE

973

Expression of Natriuretic Peptide in Ventricular Myocardium of Failing Human Hearts and Its Correlation with the Severity of Clinical and Hemodynamic Impairment

Eloisa Arbustini, Angela Pucci, Maurizia Grasso, Marta Diegoli, Roberto Pozzi, Antonello Gavazzi, Gabriella Graziano, Carlo Campana, Claudio Goggi, Luigi Martinelli, Enrico Silini, Giuseppe Specchia, Mario Vigano, and Enrico Solcia

Atrial natriuretic peptide (ANP) was immunohistochemically investigated: (1) in right ventricular endomyocardial biopsy specimens from 87 apparently healthy donor hearts; (2) from 151 patients with dilated cardiomyopathy (DC), (3) in 1 apparently healthy donor heart not suitable for transplantation (HBsAg carrier), and (4) in 57 explanted hearts, 26 with DC and 31 with ischemic heart disease. No ANP immunoreactivity was found in normal ventricles. Failing hearts showed ventricular ANP reactivity in 31% of the DC biopsy series, in 61% of the left ventricles, and in 30% of the right ventricles of the explanted heart series. At ultrastructural investigation, endocrine granules in ventricular myocytes were not detected in 10 normal donor biopsy samples, whereas ANP granules were seen in 15 of 132 (11.4%) DC cases. In parallel immunoblotting, investigation showed the same 13 kDa band protein in 1 normal atrium as well as in 8 failing atria and ventricles. ANP immunoreactivity was positively correlated with more symptomatic patients (higher New York Heart Association functional classes) as well as with higher end-diastolic pressure, and end-diastolic volume and index. In conclusion, normal ventricles do not express ANP immunoreactivity, whereas failing ventricles do. Ventricular ANP reactivity seems to be unrelated to the underlying disease, but strictly dependent on the degree of left ventricular dysfunction.

981

Usefulness of Verapamil for Congestive Heart Failure Associated with Abnormal Left Ventricular Diastolic Filling and Normal Left Ventricular Systolic Performance

John F. Setaro, Barry L. Zaret, Douglas S. Schulman, Henry R. Black, and Robert Soufer

A substantial number of patients with heart failure exhibit normal systolic function with impaired diastolic performance. We studied 20 patients in this subset, treating them with oral verapamil or placebo in a crossover trial. Evaluation included clinical scoring, exercise testing and radionuclide analysis of ventricular filling. Active ischemia was excluded by thallium-201 stress scintigraphy. Verapamil therapy resulted in significant improvement in all 3 indexes without a decrease in ejection fraction. This study suggests a role for verapamil in treating patients with heart failure and selectively impaired diastolic function.

Continued on page A47

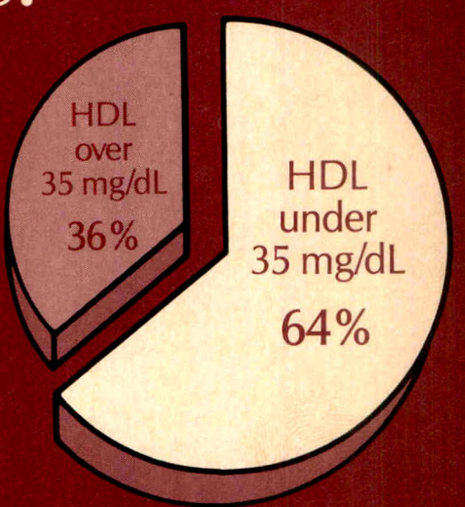
≥240 TOTAL

<35 HDL

What's a common denominator of most heart attack victims?

Mixed hyperlipidemias—elevated cholesterol *and* triglycerides—are common among heart attack victims,[1] and nearly two thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.[2]

HEART ATTACK PATIENTS (PROCAM TRIAL)[2]



LOPID raised low HDL 25%

—in patients whose baseline HDL was below 35 mg/dL in the landmark Helsinki Heart Study (HHS).[3]

Reduced heart attack incidence* up to 62%

—in these HHS patients and 45% in HHS patients whose baseline HDL was below the median (46.4 mg/dL). Incidence of serious coronary events was similar for LOPID and placebo subgroups with baseline HDL above the median (46.4 mg/dL).[3]

A powerful case for LOPID®



BID

(gemfibrozil) 600-mg Tablets

RAISES HDL...DRAMATICALLY REDUCES HEART ATTACK

LOPID is indicated for reducing the risk of coronary heart disease (CHD) in Type IIb patients with low HDL, in addition to elevated LDL and triglycerides, and who have had an inadequate response to weight loss, diet, exercise, and other pharmacologic agents such as bile acid sequestrants and nicotinic acid.

*Defined as a combination of definite coronary death and/or definite myocardial infarction.

References: 1. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. *J Clin Invest.* 1973;52:1533-1543. **2.** Assmann G, Schulte H. *PROCAM-Trial: Prospective Cardiovascular Münster Trial*. Zürich: Panscientia Verlag; 1986:8-9. **3.** Data on file, Medical Affairs Dept, Parke-Davis.

Please see adjacent page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

PARKE-DAVIS

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Lopid® (Gemfibrozil Capsules and Tablets)

Before prescribing, please see full prescribing information.
A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts—Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy**—Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy**—Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions**—(A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility**—Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

Lopid® (Gemfibrozil Capsules and Tablets)

from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children**—Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

References: 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-1245. 2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651. 3. Nikkila EA. Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J. B. et al. (eds.): *The Metabolic Basis of Inherited Disease*, 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642.

Caution—Federal law prohibits dispensing without prescription.

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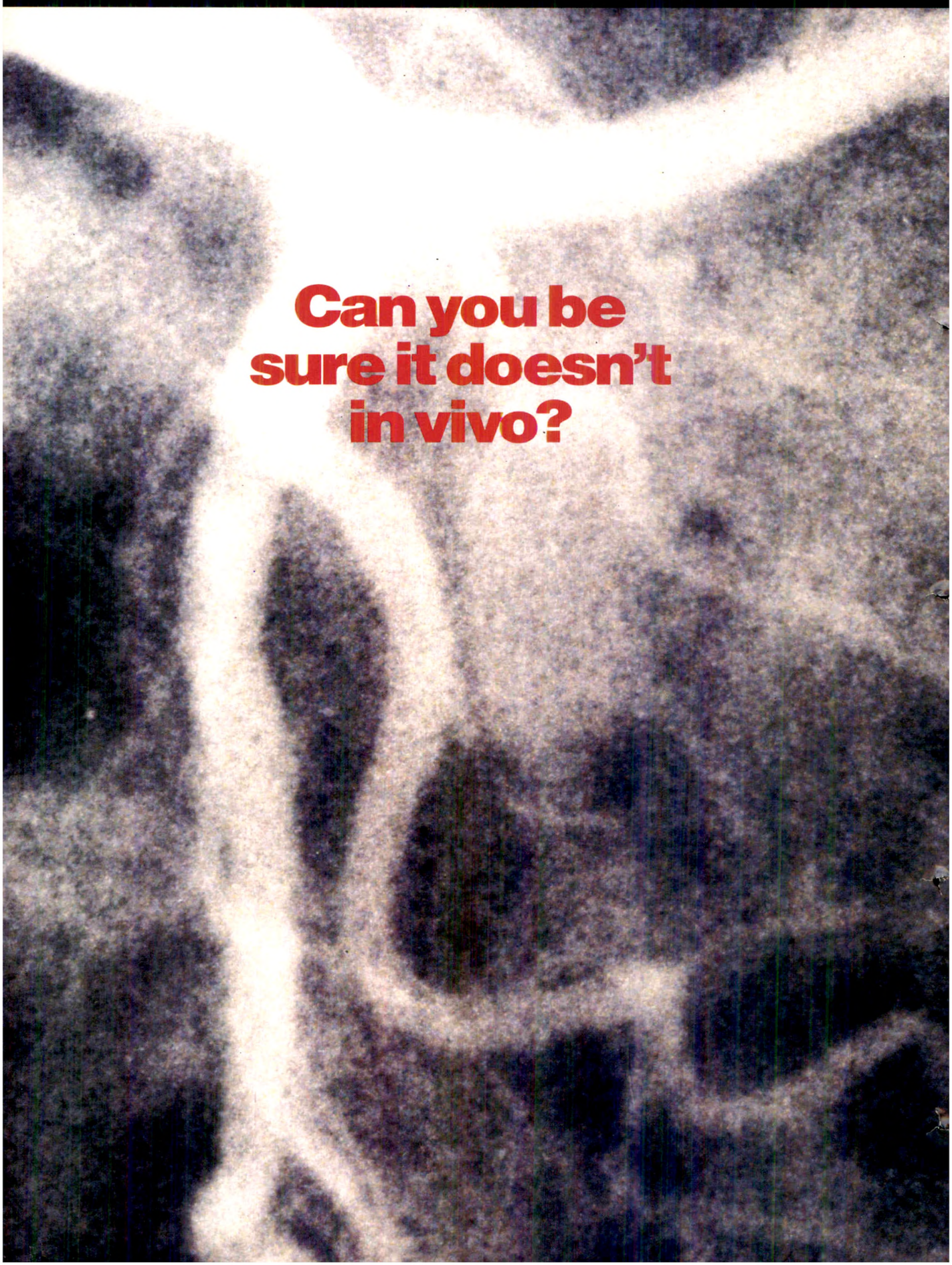
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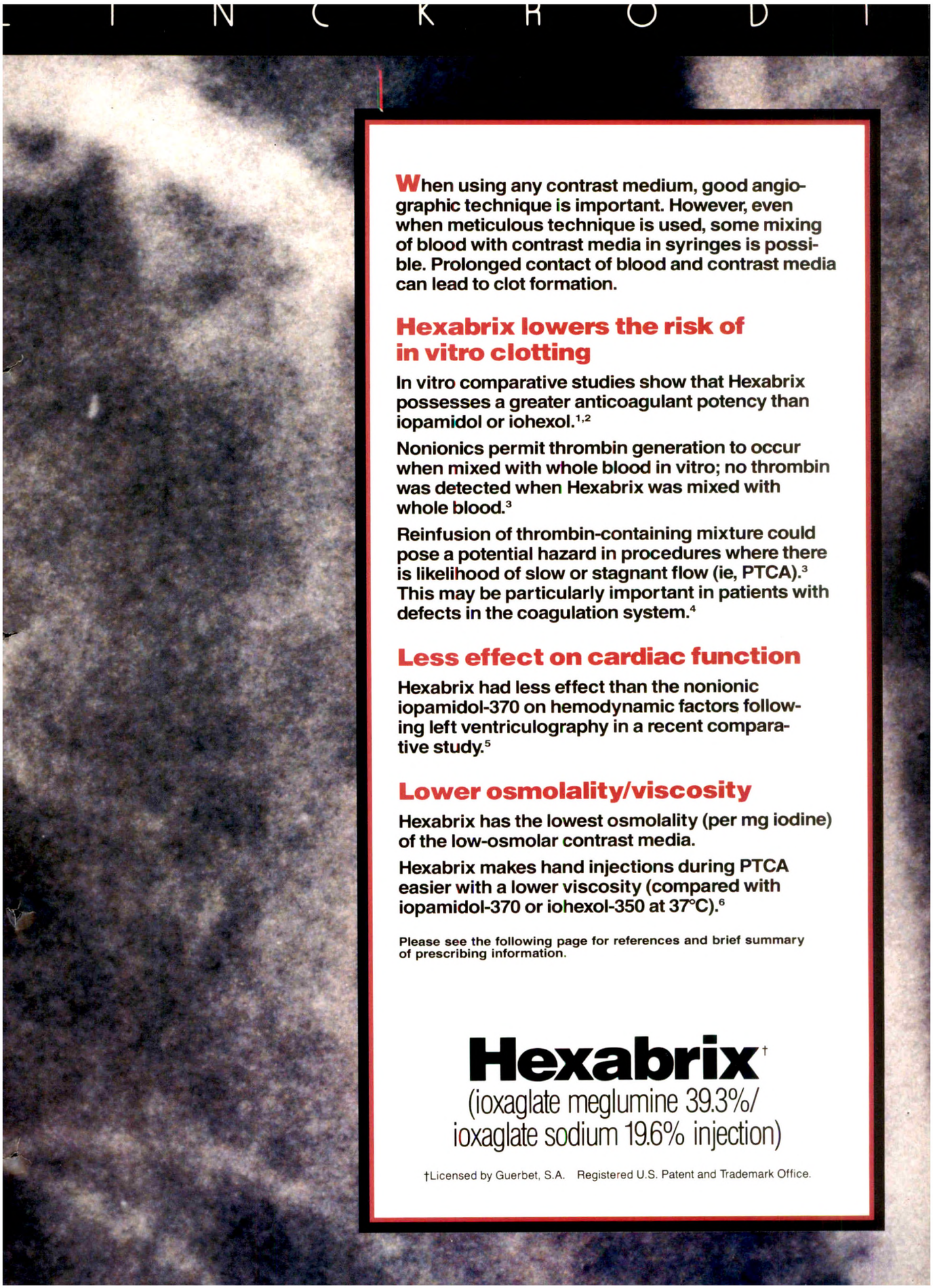
FROM MALLINCKRODT



Clotting: It happens in vitro.

F R O M M A L





When using any contrast medium, good angiographic technique is important. However, even when meticulous technique is used, some mixing of blood with contrast media in syringes is possible. Prolonged contact of blood and contrast media can lead to clot formation.

Hexabrix lowers the risk of in vitro clotting

In vitro comparative studies show that Hexabrix possesses a greater anticoagulant potency than iopamidol or iohexol.[1,2]

Nonionics permit thrombin generation to occur when mixed with whole blood in vitro; no thrombin was detected when Hexabrix was mixed with whole blood.[3]

Reinfusion of thrombin-containing mixture could pose a potential hazard in procedures where there is likelihood of slow or stagnant flow (ie, PTCA).[3] This may be particularly important in patients with defects in the coagulation system.[4]

Less effect on cardiac function

Hexabrix had less effect than the nonionic iopamidol-370 on hemodynamic factors following left ventriculography in a recent comparative study.[5]

Lower osmolality/viscosity

Hexabrix has the lowest osmolality (per mg iodine) of the low-osmolar contrast media.

Hexabrix makes hand injections during PTCA easier with a lower viscosity (compared with iopamidol-370 or iohexol-350 at 37°C).[6]

Please see the following page for references and brief summary of prescribing information.

Hexabrix†
(ioxaglate meglumine 39.3%/
ioxaglate sodium 19.6% injection)

†Licensed by Guerbet, S.A. Registered U.S. Patent and Trademark Office.

Hexabrix† (ioxaglate meglumine 39.3%/ioxaglate sodium 19.6% injection)

HEXABRIX®

ach milliliter of HEXABRIX contains 393 mg of ioxaglate
neglumine, 196 mg of ioxaglate sodium and 0.10 mg edetate
alcium disodium as a stabilizer. The solution contains 3.48
ng (0.15 mEq) sodium in each milliliter and provides 32%
320 mg/mL) organically bound iodine.

CONTRAINDICATIONS

IEXABRIX is contraindicated for use in myelography. Refer to
'RECAUTIONS concerning hypersensitivity. Hysterosalpin-
iography should not be performed during the menstrual
eriod; in pregnant patients; in patients with known infection
any portion of the genital tract; or in patients in whom
ervical conization or curettage has been performed within
0 days. Arthrography should not be performed if infec-
on is present in or near the joint.

WARNINGS

onic iodinated contrast media inhibit blood coagulation, *in
itro*, more than nonionic contrast media. Nonetheless, it is
rudent to avoid prolonged contact of blood with syringes con-
aining ionic contrast media.

Serious, rarely fatal, thromboembolic events causing
nyocardial infarction and stroke have been reported during
ngiographic procedures with both ionic and nonionic contrast
nedia. Therefore, meticulous intravascular administration
echnique is necessary, particularly during angiographic pro-
edures, to minimize thromboembolic events. Numerous
actors, including length of procedure, catheter and syringe
naterial, underlying disease state, and concomitant medica-
ions may contribute to the development of thromboembolic
vents. For these reasons, meticulous angiographic tech-
iques are recommended including close attention to guide-
ire and catheter manipulation, use of manifold systems
nd/or three-way stopcocks, frequent catheter flushing
ith heparinized saline solutions and minimizing the length
f the procedure. The use of plastic syringes in place of glass
yringes has been reported to decrease but not eliminate
he likelihood of *in vitro* clotting.

As with any contrast medium, serious neurologic sequelae,
cluding permanent paralysis, can occur following cerebral
teriography, selective spinal arteriography and arteriography
vessels supplying the spinal cord. The injection of a contrast
edium should never be made following the administration
vasopressors, since they strongly potentiate neuro-
gic effects.

In patients with subarachnoid hemorrhage, a rare associa-
on between contrast administration and clinical deterioration,
cluding convulsions and death, has been reported.
herefore, administration of intravascular iodinated contrast
edia in these patients should be undertaken with caution.

*A definite risk exists in the use of intravascular contrast
ents in patients who are known to have multiple myeloma.* In
ch instances anuria has developed, resulting in progressive
emia, renal failure and eventually death. Although neither the
ntrast agent nor dehydration has separately proved to be the
use of anuria in myeloma, it has been speculated that the
mbination of both may be a causative factor. The risk in
yelomatous patients is not a contraindication to the pro-
dure; however, partial dehydration in the preparation of
ese patients for the examination is not recommended since
is may predispose to precipitation of myeloma protein in
e renal tubules. No form of therapy, including dialysis, has
en successful in reversing the effect. Myeloma, which
curs most commonly in persons over 40, should be con-
dered before instituting intravascular administration of
ntrast agents.

*Administration of radiopaque materials to patients known
suspected to have pheochromocytoma should be per-
rmed with extreme caution.* If, in the opinion of the
ysician, the possible benefits of such procedures outweigh
e considered risks, the procedures may be performed;
wever, the amount of radiopaque medium injected should
kept to an absolute minimum. The blood pressure should be
essed throughout the procedure, and measures for treat-
ent of a hypertensive crisis should be available.

Since intravascular administration of contrast media may
omote sickling in individuals who are homozygous for sickle
ll disease, fluid restriction is not advised.

In patients with advanced renal disease, iodinated contrast
edia should be used with caution and only when the need for
e examination dictates, since excretion of the medium may
impaired. Patients with combined renal and hepatic
isease, those with severe hypertension or congestive heart
lure and recent renal transplant recipients present an
ditional risk.

Renal failure has been reported in patients with liver
sfunction who were given an oral cholecystographic agent
llowed by an intravascular iodinated radiopaque agent and
o in patients with occult renal disease, notably diabetics and
pertensives. In these classes of patients there should be no
id restriction and every attempt made to maintain normal
dration prior to contrast medium injection, since dehydra-
n is the single most important factor influencing further
al impairment.

Caution should be exercised in performing contrast
edium studies in patients with endotoxemia and/or those
h elevated body temperatures.

Reports of thyroid storm occurring following the intra-
scular use of iodinated radiopaque agents in patients with
perthyroidism or with an autonomously functioning thyroid
dule, suggest that this additional risk be evaluated before
e of this drug. Iodine-containing contrast agents may alter
results of thyroid function tests which depend on iodine
imation, e.g., PBI, and may also affect results of radioactive
ine uptake studies. Such tests, if indicated, should be per-
med prior to the administration of this preparation.

PRECAUTIONS

gnostic procedures which involve the use of iodinated
avascular contrast agents should be carried out under the
ction of personnel skilled and experienced in the particular
cedure to be performed. All procedures utilizing contrast
dia carry a definite risk of producing adverse reactions.
ile most reactions are minor, life-threatening and fatal reac-
is may occur without warning, and this risk must be
ghed against the benefit of the procedure. A fully equipped
ergency cart, or equivalent supplies and equipment, and
sonnel competent in recognizing and treating adverse reac-
is of all types should always be available. If a serious reac-
should occur, immediately discontinue administration.
e severe delayed reactions have been known to occur,
ergency facilities and competent personnel should be avail-
for at least 30 to 60 minutes after administration. (See
VERSE REACTIONS.)

Preparatory dehydration is dangerous and may contribute
cute renal failure in infants, young children, the elderly,
patients with pre-existing renal insufficiency, patients with
multiple myeloma, patients with advanced vascular disease
and diabetic patients.

Acute renal failure has been reported in diabetic patients
with diabetic nephropathy and in susceptible non-diabetic
patients (often elderly with pre-existing renal disease) follow-
ing the administration of iodinated contrast agents. Therefore,
careful consideration of the potential risks should be given be-
fore performing this radiographic procedure in these patients.

Severe reactions to contrast media often resemble allergic
responses. This has prompted the use of several provocative
pretesting methods, none of which can be relied on to predict
severe reactions. No conclusive relationship between severe
reactions and antigen-antibody reactions or other man-
ifestations of allergy has been established. The possibility of an
idiosyncratic reaction in patients who have previously received
a contrast medium without ill effect should always be consid-
ered. Prior to the injection of any contrast medium, the patient
should be questioned to obtain a medical history with empha-
sis on allergy and hypersensitivity. A positive history of bron-
chial asthma or allergy (including food), a family history of
allergy, or a previous reaction or hypersensitivity to a contrast
agent may imply a greater than usual risk. Such a history may
be more accurate than pre-testing in predicting the potential for
reaction, although not necessarily the severity or type of reac-
tion in the individual case. A positive history of this type does
not arbitrarily contraindicate the use of a contrast agent when a
diagnostic procedure is thought essential, but does call for
caution. (See ADVERSE REACTIONS.)

Prophylactic therapy including corticosteroids and anti-
histamines should be considered for patients who present with
a strong allergic history, a previous reaction to a contrast
medium, or a positive pre-test since in these patients the inci-
dence of reaction is two to three times that of the general
population. Adequate doses of corticosteroids should be
started early enough prior to contrast medium injection to be
effective and should continue through the time of injection and
for 24 hours after injection. Antihistamines should be adminis-
tered within 30 minutes of the contrast medium injection.
Recent reports indicate that such pre-treatment does not
prevent serious life-threatening reactions, but may reduce
both their incidence and severity. A separate syringe should be
used for these injections.

General anesthesia may be indicated in the performance of
some procedures in selected patients; however, a higher
incidence of adverse reactions has been reported in these
patients, and may be attributable to the inability of the patient
to identify untoward symptoms or to the hypotensive effect of
anesthesia which can prolong the circulation time and increase
the duration of contact of the contrast agent.

Angiography should be avoided whenever possible in
patients with homocystinuria because of the risk of inducing
thrombosis and embolism.

PRECAUTIONS FOR SPECIFIC PROCEDURES

Pediatric Angiocardiography: It is advisable to monitor for
ECG and vital signs changes throughout the procedure.

When large individual doses are administered, sufficient
time should be allowed for any observed changes to return to
or near baseline prior to making the next injection.

Caution should be used when making right heart injections
in patients with pulmonary hypertension or incipient heart fail-
ure, since this may lead to increased right side pressures with
subsequent bradycardia and systemic hypotension. Patients
with pulmonary disease present additional risks.

Caution is advised in cyanotic infants since apnea,
bradycardia, other arrhythmias and a tendency to acidosis are
more likely to occur.

Since infants are more likely to respond with convulsions
than are adults, the amount of total dosage is of particular
importance. Repeated injections are hazardous in infants
weighing less than 7 kg, particularly when these infants have
pre-existing compromised right heart function or obliterated
pulmonary vascular beds.

*Selective Coronary Arteriography with or without left
ventriculography:* During the administration of large doses of
HEXABRIX, continuous monitoring of vital signs is desirable.
Caution is advised in the administration of large volumes to
patients with incipient heart failure because of the possibility of
aggravating the pre-existing condition. Hypotension should be
corrected promptly since it may result in serious arrhythmias.

Special care regarding dosage should be observed in
patients with right ventricular failure, pulmonary hyper-
tension, or stenotic pulmonary vascular beds because of
hemodynamic changes which may occur after injection into
the right heart outflow tract.

Peripheral Arteriography: Moderate decreases in blood
pressure occur frequently with intra-arterial (brachial) in-
jections. This change is usually transient and requires no
treatment; however, the blood pressure should be monitored
for approximately ten minutes following injection.

Extreme caution during injection of the contrast agent is
necessary to avoid extravasation and fluoroscopy is rec-
ommended. This is especially important in patients with
severe arterial disease.

Cerebral Angiography: Cerebral angiography should be
performed with special caution in patients with advanced
arteriosclerosis, severe hypertension, cardiac decompen-
sation, senility, recent cerebral thrombosis or embolism, and
migraine.

Intra-Arterial Digital Subtraction Angiography: The risks
associated with IA-DSA are those usually attendant with cathe-
ter procedures. Following the procedure, gentle pressure
hemostasis is required, followed by observation and
immobilization of the limb for several hours to prevent
hemorrhage from the site of arterial puncture.

Patient motion, including respiration and swallowing, can
result in misregistration leading to image degradation and
non-diagnostic studies.

Intravenous Digital Subtraction Angiography: The risks
associated with IV-DSA include those usually attendant with
catheter procedures and include intramural injections, vessel
dissection and tissue extravasation. The potential risk is re-
duced when small test injections of contrast medium are made
under fluoroscopic observation to insure that the catheter tip is
properly positioned and, in the case of peripheral placement,
that the vein is of adequate size.

Patient motion, including respiration and swallowing, can
result in misregistration leading to image degradation and
non-diagnostic studies.

Peripheral Venography: Special care is required when
venography is performed in patients with suspected
thrombosis, phlebitis, severe ischemic disease, local infection
or a totally obstructed venous system.

Extreme caution during injection of contrast media
is necessary to avoid extravasation and fluoroscopy is
recommended. This is especially important in patients with
severe arterial or venous disease.

Excretory Urography: Infants and small children should
not have any fluid restrictions prior to excretory urography.
(See WARNINGS and PRECAUTIONS concerning preparatory
dehydration.)

Contrast Enhancement in Body Computed Tomography:
Patient cooperation is essential since patient motion, including
respiration, can markedly affect image quality. The use of an
intravascular contrast medium can obscure tumors in patients
undergoing CT evaluation of the liver, resulting in a false nega-
tive diagnosis. Dynamic CT scanning is the procedure of
choice for malignant tumor enhancement.

Arthrography: Strict aseptic technique is required to pre-
vent the introduction of infection. Fluoroscopic control should
be used to insure proper introduction of the needle into the
synovial space and prevent extracapsular injection. Aspiration
of excessive synovial fluid will reduce the pain on injection and
prevent the dilution of the contrast agent. It is important that
undue pressure not be exerted during the injection.

Hysterosalpingography: Caution should be exercised in
patients suspected of having cervical or tubal carcinoma to
avoid possible spread of the lesion by the procedure.
Delayed onset of pain and fever (1-2 days) may be indicative of
pelvic infection.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No
long-term animal studies have been performed to evaluate
carcinogenic potential. However, animal studies suggest that
this drug is not mutagenic and does not affect fertility in males
or females.

Pregnancy Category B: Reproduction studies have been
performed in rats and rabbits at doses up to two times the
maximum adult human dose and have revealed no evidence of
impaired fertility or harm to the fetus due to HEXABRIX. There
are, however, no adequate and well controlled studies in preg-
nant women. Because animal reproduction studies are not
always predictive of human response, this drug should be
used during pregnancy only if clearly needed.

Nursing Mothers: Ioxaglate salts are excreted unchanged in
human milk. Because of the potential for adverse effects in
nursing infants, bottle feedings should be substituted for
breast feedings for 24 hours following the administration of
this drug.

Pediatric Use: Safety and effectiveness in children has been
established in pediatric angiocardiography and intravenous
excretory urography. Data have not been submitted to sup-
port the safety and effectiveness of HEXABRIX in any other
indication.

(Precautions for specific procedures receive comment
under that procedure.)

ADVERSE REACTIONS

Adverse reactions to injectable contrast media fall into two
categories: chemotoxic reactions and idiosyncratic reactions.

Chemotoxic reactions result from the physiochemical
properties of the contrast media, the dose and the speed
of injection. All hemodynamic disturbances and injuries
to organs or vessels perfused by the contrast medium are
included in this category.

Idiosyncratic reactions include all other reactions. They
occur more frequently in patients 20 to 40 years old.
Idiosyncratic reactions may or may not be dependent on the
dose injected, the speed of injection, the mode of injection and
the radiographic procedure. Idiosyncratic reactions are
subdivided into minor, intermediate and severe. The minor
reactions are self-limited and of short duration; the severe
reactions are life-threatening and treatment is urgent and
mandatory.

NOTE: Not all of the following adverse reactions have been
reported with HEXABRIX. Because HEXABRIX is an iodinated
intravascular contrast agent, all of the side effects and toxicity
associated with agents of this class are theoretically possible,
and this should be borne in mind when HEXABRIX is
administered.

Severe, life-threatening anaphylactoid reactions, mostly of
cardiovascular origin, have occurred following the administra-
tion of HEXABRIX as well as other iodine-containing contrast
agents. Most deaths occur during injection or 5 to 10 minutes
later; the main feature being cardiac arrest with cardiovascular
disease as the main aggravating factor. Isolated reports of
hypotensive collapse and shock are found in the literature.
Based upon clinical literature, reported deaths from the
administration of conventional iodinated contrast agents
range from 6.6 per 1 million (0.00066 percent) to 1 in
10,000 patients (0.01 percent).

Regardless of the contrast agent employed, the overall
estimated incidence of serious adverse reactions is higher
with coronary arteriography than with other procedures.
Cardiac decompensation, serious arrhythmias, or myo-
cardial ischemia or infarction may occur during coronary
arteriography and left ventriculography.

The most frequent adverse reactions are nausea, vomiting,
facial flush and a feeling of body warmth. These are usually of
brief duration. In double-blind clinical trials, HEXABRIX pro-
duced less discomfort upon injection (pain and heat) when
compared to various other contrast agents. Other reactions
include the following:

Hypersensitivity reactions: Dermal manifestations of
urticaria with or without pruritus, erythema and maculopapu-
lar rash. Dry mouth. Sweating. Conjunctival symptoms.
Facial, peripheral and angioneurotic edema. Symptoms
related to the respiratory system include sneezing, nasal
stuffiness, coughing, choking, dyspnea, chest tightness and
wheezing, which may be initial manifestations of more severe
and infrequent reactions including asthmatic attack, laryngo-
spasm and bronchospasm with or without edema, pulmonary
edema, apnea and cyanosis. Rarely, these allergic-type
reactions can progress into anaphylaxis with loss of con-
sciousness, coma, severe cardiovascular disturbances,
and death.

Cardiovascular reactions: Generalized vasodilation, flush-
ing and venospasm. Occasionally thrombosis or, rarely,
thrombophlebitis. Extremely rare cases of disseminated
intravascular coagulation resulting in death have been
reported. Severe cardiovascular responses include rare cases
of hypotensive shock, coronary insufficiency, cardiac
arrhythmia, fibrillation and arrest. These severe reactions are
usually reversible with prompt and appropriate management;
however, fatalities have occurred.

Technique reactions: Extravasation with burning pain,
hematomas, ecchymosis and tissue necrosis, vascular
constriction due to injection rate, thrombosis and
thrombophlebitis.

Neurological reactions: Spasm, convulsions, aphasia, syn-
cope, paresis, paralysis resulting from spinal cord injury and
pathology associated with the syndrome of transverse
myelitis, visual field losses which are usually transient but may
be permanent, coma and death.

Other reactions: Headache, trembling, shaking, chills
without fever, hyperthermia and lightheadedness. Temporary
renal shutdown or other nephropathy.

Pediatric angiocardiography has been complicated by
intramural injection with marked adverse effects on cardiac
function.

During selective coronary arteriography with or without left
ventriculography, patients may have clinically insignificant
ECG changes. The following adverse effects have occurred in
conjunction with the administration of iodinated intravascular
contrast agents for this procedure: hypotension, shock,
anginal pain, myocardial infarction, cardiac arrhythmias
(bradycardia, ventricular tachycardia, ventricular fibrillation)
and cardiac arrest. Fatalities have been reported. Com-
plications to the procedure include dissection of coronary
arteries, dislodgement of atheromatous plaques, perforation,
hemorrhage and thrombosis.

Following peripheral arteriography, hemorrhage and
thrombosis have occurred at the puncture site of the per-
cutaneous injection. Brachial plexus injury has been reported
following axillary artery injection.

The major causes of cerebral arteriographic adverse reac-
tions appear to be repeated injections of the contrast material,
administration of doses higher than those recommended, the
presence of occlusive atherosclerotic vascular disease and the
method and technique of injection. Adverse reactions are nor-
mally mild and transient. A feeling of warmth in the face and
neck is frequently experienced. Infrequently, a more severe
burning discomfort is observed. Transient visual hallucina-
tions have been reported. Serious neurological reactions that
have been associated with cerebral angiography and not listed
under Adverse Reactions include stroke, amnesia and respira-
tory difficulties. Visual field defects with anopsia and reversible
neurological deficit lasting from 24 hours to 48 hours have
been reported. Confusion, disorientation with hallucination,
and absence of vision sometimes lasting for one week have
also been reported. Cardiovascular reactions that may occur
with some frequency are bradycardia and either an increase or
decrease in systemic blood pressure. The blood pressure
change is transient and usually requires no treatment.
Arthrography may induce joint pain or discomfort which is
usually mild and transient but occasionally may be severe
and persist for 24 to 48 hours following the procedure.
Effusion requiring aspiration may occur in patients with
rheumatoid arthritis. Fever and pain, cramping and tender-
ness of the abdomen have been reported following
hysterosalpingography.

OVERDOSAGE

Overdosages may occur. The adverse effects of overdosage
are life-threatening and affect mainly the pulmonary and car-
diovascular systems. The symptoms may include cyanosis,
bradycardia, acidosis, pulmonary hemorrhage, convulsions,
coma and cardiac arrest. Treatment of an overdose is directed
toward the support of all vital functions and prompt institution
of symptomatic therapy.

Ioxaglate salts are dialyzable.

The intravenous LD_{50} values of HEXABRIX (in grams
of iodine/kilogram body weight) were 11.2 g/kg in mice,
> 8 g/kg in rats, >6.4 g/kg in rabbits and > 10.2 g/kg
in dogs.

DOSAGE AND ADMINISTRATION

Details on dosage are provided in the package insert. *CON-
SULT FULL PACKAGE INSERT BEFORE USE.*

Rev. Nov. 1989

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Changes in Circulating Norepinephrine with Hemofiltration in Advanced Congestive Heart Failure

Carlo M. Cipolla, Sergio Grazi, Andrea Rimondini, Giuseppe Susini, Marco Guazzi, Paolo Della Bella, and Maurizio D. Guazzi

In cases of advanced congestive heart failure (CHF) with fluid retention, filtration of plasma water (2,983 ml) greatly decreased the elevated levels of plasma norepinephrine. Despite this, the associated hemodynamic variations were negligible, suggesting that in CHF the elevation of the circulating sympathetic transmitter does not contribute significantly to the hemodynamic control and probably does not reflect the intensity of the neural activity. The norepinephrine decrease was proportional to the potentiation of the urinary output promoted by hemofiltration. This procedure might augment removal of norepinephrine from plasma by relieving congestion of organs (lung and kidney) endowed with a high extraction rate of the neurotransmitter. Thus, a reduced clearance of norepinephrine due to retention of fluid may importantly contribute to the increase of circulating norepinephrine in CHF.

MISCELLANEOUS

995

Effects of Preload Reduction on Mitral Flow Velocity Pattern in Normal Subjects

Marco O. Triulzi, Diego Castini, Maurizio Ornaghi, and Erminio Vitolo

Atrioventricular pressure gradient is one of the major determinants of mitral blood flow. Changes in preload should affect the atrioventricular pressure gradient and, consequently, the mitral blood flow pattern. The purpose of this study was to evaluate the effects of systemic venous return reduction on mitral flow velocities by Doppler echocardiography. We studied 12 normal subjects in the basal state and after a 5-minute period of pressure cuffs inflation on the 4 limbs. A significant decrease of peak E-wave velocity was observed with no significant changes of the peak A-wave velocity; this resulted in significant reduction of the E/A peak velocity. Thus, preload reduction in normal subjects determines a mitral flow velocity pattern that mimics the changes already observed in left ventricular diastolic dysfunction.

1002

Clinical and Hemodynamic Assessment of the Hepatojugular Reflux

Randall A. Sochowski, James D. Dubbin, and Salim Z. Naqvi

The hepatojugular reflux (HJR) test was studied at the bedside and during right-sided cardiac catheterization in 65 patients clinically considered to be free of heart failure. The HJR test required only 15 seconds of observation for interpretation in 62 of the 65 patients. The test result at the bedside agreed with the result during catheterization ($\kappa = 0.74$, $p < 0.001$). A positive test could detect elevated right-sided heart pressures

and was sensitive and specific for predicting right atrial pressure >9 mm Hg and right ventricular end-diastolic pressure >12 mm Hg. The strongest correlation of the HJR test was to the baseline mean right atrial pressure ($r = 0.59$) and right ventricular end-diastolic pressure ($r = 0.51$); in bivariate regression analysis the test best predicted these 2 hemodynamic variables. This suggests a central role of right-sided cardiac function in determining the response.

METHODS

1007
Anatomic Correlations of the Long-Axis Views in Biplane Transesophageal Echocardiography
Gerald I. Cohen, Kwan-Leung Chan, and Virginia M. Walley

A newly available biplane transesophageal echocardiographic probe is capable of imaging in the long-axis plane in addition to the familiar short-axis plane. This study defined 6 standard views of the heart and great vessels obtainable with long-axis imaging. These views were compared with corresponding anatomic sections to illustrate anatomic relations and facilitate structure identification.

BRIEF REPORTS

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Circadian Fluctuations in Ventricular Response to Atrial Fibrillation
Ernst A. Raeder

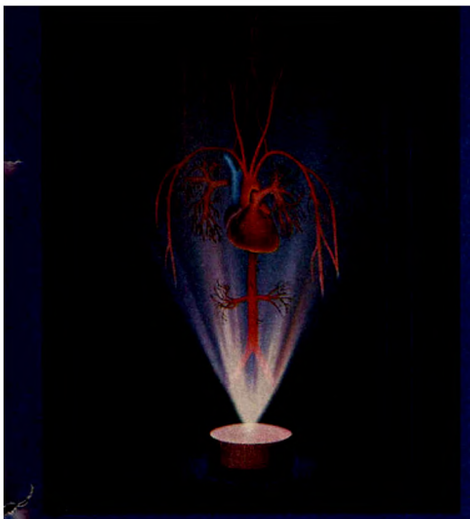
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Comparison of Indications for Aortic Valve Replacement in 1978 and in 1988
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Once-a-Day

Procardia XL®

(nifedipine) Extended Release

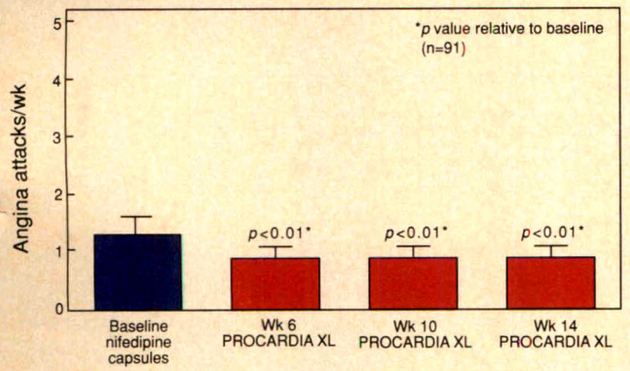
Tablets **30** mg, **60** mg and **90** mg **GITS**

The convenience of a once-a-day calcium channel blocker

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The effectiveness you expect from nifedipine for a full 24 hours

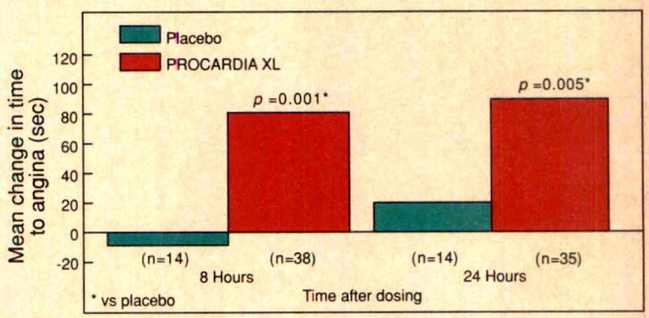
ANGINA FREQUENCY[1]



Fourteen-week, open-label, crossover trial to compare the efficacy and dose equivalence of nifedipine capsules (weeks 1 and 2) vs PROCARDIA XL (weeks 3-14) in 98 patients with chronic stable angina who had been on nifedipine capsules at least one month prior to the study. Patients were switched to the nearest equivalent daily dose over the dose range of 30-150 mg/day. Ninety-five patients were crossed over to receive PROCARDIA XL; 91 of these were evaluated for efficacy. The majority remained on beta blockers and/or nitrates throughout the study. (Reported by Vetrovec GW et al, *Am J Med*, 1987.[1])

Patients were of different races. (Data on file. Medical Department, Pfizer Labs, Pfizer Inc.[2])

TIME TO ANGINA[3]

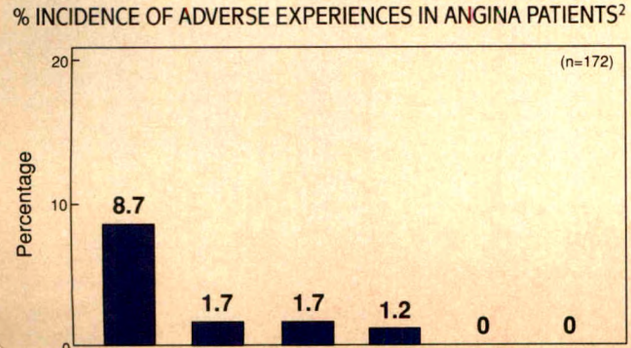


Double-blind, randomized, placebo-controlled, dose-response study. Patients were randomized to receive one of four treatments: PROCARDIA XL at a dose of 30, 60 or 90 mg qd plus beta blocker or placebo plus beta blocker. Exercise testing was performed at 8 and 24 hours post dose at the end of a 2-week baseline phase and a 2-week efficacy phase. (Reported by Bittar N, *Am J Cardiol*, 1989.[3])

Baseline time to angina was 290 sec. Baseline by dosage: 30 mg—269 sec; 60 mg—314 sec; 90 mg—254 sec. At the end of the efficacy phase, exercise-induced angina was present in 38 of 46 patients randomized to PROCARDIA XL and in 14 of 17 patients randomized to placebo. Patient population was predominantly white. (Data on file. Medical Department, Pfizer Labs, Pfizer Inc.[2])

...With a low incidence of vasodilatory side effects[2]

% INCIDENCE OF ADVERSE EXPERIENCES IN ANGINA PATIENTS[2]



Data obtained from multiple controlled trials of PROCARDIA XL (30-150 mg qd) in 172 patients with angina. (Data on file. Medical Department, Pfizer Labs, Pfizer Inc.[2])

- The most common side effects are peripheral edema, which is not associated with fluid retention, and headache

  In controlled studies of 776 patients with PROCARDIA XL, edema resulted in discontinuation of therapy in 2.7% of patients[2]

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Please see brief summary of prescribing information on adjacent page.

Once-a-Day

Procardia XL®

(nifedipine) Extended Release

Tablets 30 mg, 60 mg and 90 mg GITS

Easy mg-for-mg switch to convenient, once-daily dosing

- Over 90% of angina patients controlled on nifedipine capsules were easily switched to and controlled on PROCARDIA XL Extended Release Tablets at the nearest equivalent total daily dose; others needed dosage adjustment [2]



One 10-mg nifedipine capsule tid



One 30-mg PROCARDIA XL Extended Release Tablet qd



One 20-mg nifedipine capsule tid



One 60-mg PROCARDIA XL Extended Release Tablet qd

Switch From Nifedipine Capsules to PROCARDIA XL Extended Release Tablets

Capsules	XL Tablets
30–40 mg/day in divided doses	→ **30 mg once a day**
50–70 mg/day in divided doses	→ **60 mg once a day**
80–100 mg/day in divided doses	→ **90 mg once a day**

- Subsequent dosage adjustments may be necessary and should be initiated as clinically warranted
- The total daily dose can be given with multiple tablets once a day, such as two 30-mg PROCARDIA XL Extended Release Tablets to equal 60 mg total daily dose
- Experience with doses >90 mg in patients with angina is limited; therefore, doses >90 mg should be used with caution and only when clinically warranted

References:

1. Vetrovec GW, Parket VE, Cole S, et al: Nifedipine gastrointestinal therapeutic system in stable angina pectoris: Results of a multicenter open-label crossover comparison with standard nifedipine. *Am J Med* 1987;83(suppl 6B):24-29.
2. Data on file. Medical Department, Pfizer Labs, Pfizer Inc, New York.
3. Bittar N: Usefulness of nifedipine for myocardial ischemia and the nifedipine gastrointestinal therapeutic system. *Am J Cardiol* 1989;64:31F-34F.

Brief Summary
PROCARDIA XL® (nifedipine) Extended Release Tablets For Oral Use

CONTRAINDICATIONS: Known hypersensitivity reaction to nifedipine.

WARNINGS: Excessive Hypotension: Although in most angina patients the hypotensive effect of nifedipine is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving nifedipine together with a beta-blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of nifedipine and a beta blocker, but the possibility that it may occur with nifedipine alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In nifedipine-treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for nifedipine to be washed out of the body prior to surgery.

The following information should be taken into account in those patients who are being treated for hypertension as well as angina:

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting nifedipine or at the time of dosage increase. The mechanism of this effect is not established.

Beta Blocker Withdrawal: It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning nifedipine. Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of nifedipine treatment will not prevent this occurrence and on occasion has been reported to increase it.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker, have developed heart failure after beginning nifedipine. Patients with tight aortic stenosis may be at greater risk for such an event, as the unloading effect of nifedipine would be expected to be of less benefit to those patients, owing to their fixed impedance to flow across the aortic valve.

PRECAUTIONS: General—Hypotension: Because nifedipine decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of nifedipine is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.)

Peripheral Edema: Mild to moderate peripheral edema occurs in a dose dependent manner with an incidence ranging from approximately 10% to about 30% at the highest dose studied (180 mg). It is a localized phenomenon thought to be associated with vasodilation of dependent arterioles and small blood vessels and not due to left ventricular dysfunction or generalized fluid retention. With patients whose angina or hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Other: As with any other non-deformable material, caution should be used when administering PROCARDIA XL in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of PROCARDIA XL.

Laboratory Tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted. The relationship to nifedipine therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms; however, cholestasis with or without jaundice has been reported. A small (5.4%) increase in mean alkaline phosphatase was noted in patients treated with PROCARDIA XL. This was an isolated finding not associated with clinical symptoms and it rarely resulted in values which fell outside the normal range. Rare instances of allergic hepatitis have been reported. In controlled studies, PROCARDIA XL did not adversely affect serum uric acid, glucose, or cholesterol. Serum potassium was unchanged in patients receiving PROCARDIA XL in the absence of concomitant diuretic therapy, and slightly decreased in patients receiving concomitant diuretics.

Nifedipine, like other calcium channel blockers, decreases platelet aggregation *in vitro*. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some nifedipine patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for these findings has been demonstrated.

Positive direct Coombs test with/without hemolytic anemia has been reported but a causal relationship between nifedipine administration and positivity of this laboratory test, including hemolysis, could not be determined.

Although nifedipine has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to nifedipine therapy is uncertain in most cases but probable in some.

Drug Interactions—Beta-adrenergic blocking agents: (See WARNINGS) Experience in over 1400 patients with Procardia® capsules in a noncomparative clinical trial has shown that concomitant administration of nifedipine and beta-blocking agents is usually well tolerated but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angina.

Long Acting Nitrates: Nifedipine may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of nifedipine with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing nifedipine to avoid possible over- or under-digitalization.

Coumarin Anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain.

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak nifedipine plasma levels (80%) and area-under-the-curve (74%), after a one week course of cimetidine at 1000 mg per day and nifedipine at 40 mg per day. Ranitidine produced smaller, non-significant increases. The effect may be mediated by the known inhibition of cimetidine on hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of nifedipine. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Nifedipine was administered orally to rats, for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. Nifedipine has been shown to be teratogenic in rats when given in doses 30 times the maximum recommended human dose. Nifedipine was embryotoxic (increased fetal resorptions, decreased fetal weight, increased stunted forms, increased fetal deaths, decreased neonatal survival) in rats, mice, and rabbits at doses of from 3 to 10 times the maximum recommended human dose. In pregnant monkeys, doses 2/3 and twice the maximum recommended human dose resulted in small placentas and underdeveloped chorionic villi. In rats, doses three times maximum human dose and higher caused prolongation of pregnancy. There are no adequate and well controlled studies in pregnant women. PROCARDIA XL® (nifedipine) Extended Release Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE EXPERIENCES: Over 1000 patients from both controlled and open trials with PROCARDIA XL Extended Release Tablets in hypertension and angina were included in the evaluation of adverse experiences. All side effects reported during PROCARDIA XL Extended Release Tablet therapy were tabulated independent of their causal relation to medication. The most common side effect reported with PROCARDIA XL was edema which was dose related and ranged in frequency from approximately 10% to about 30% at the highest dose studied (180 mg). Other common adverse experiences reported in placebo-controlled trials include: headache (15.8%, compared to 9.8% placebo incidence), fatigue (5.9%, compared to 4.1% placebo incidence), dizziness (4.1%, compared to 4.5% placebo incidence), constipation (3.3%, compared to 2.3% placebo incidence), and nausea (3.3%, compared to 1.9% placebo incidence). Of these, only edema and headache were more common in PROCARDIA XL patients than placebo patients.

The following adverse reactions occurred with an incidence of less than 3.0%. With the exception of leg cramps, the incidence of these side effects was similar to that of placebo alone: *body as a whole/systemic*: asthenia, flushing, pain; *cardiovascular*: palpitations; *central nervous system*: insomnia, nervousness, paresthesia, somnolence; *dermatologic*: pruritus, rash; *gastrointestinal*: abdominal pain, diarrhea, dry mouth, dyspepsia, flatulence; *musculoskeletal*: arthralgia, leg cramps; *respiratory*: chest pain (nonspecific), dyspnea; *urogenital*: impotence, polyuria.

Other adverse reactions were reported sporadically with an incidence of 1.0% or less. These include: *body as a whole/systemic*: face edema, fever, hot flashes, malaise, periorbital edema, rigors; *cardiovascular*: arrhythmia, hypotension, increased angina, tachycardia, syncope; *central nervous system*: anxiety, ataxia, decreased libido, depression, hypertonia, hypoesthesia, migraine, paroniria, tremor, vertigo; *dermatologic*: alopecia, increased sweating, urticaria, purpura; *gastrointestinal*: eructation, gastroesophageal reflux, gum hyperplasia, melena, vomiting, weight increase; *musculoskeletal*: back pain, gout, myalgias; *respiratory*: coughing, epistaxis, upper respiratory tract infection, respiratory disorder, sinusitis; *special senses*: abnormal lacrimation, abnormal vision, taste perversion, tinnitus; *urogenital/reproductive*: breast pain, dysuria, hematuria, nocturia.

Adverse experiences which occurred in less than 1 in 1000 patients cannot be distinguished from concurrent disease states or medications.

The following adverse experiences, reported in less than 1% of patients, occurred under conditions (e.g., open trials, marketing experience) where a causal relationship is uncertain: gastrointestinal irritation, gastrointestinal bleeding.

In multiple-dose U.S. and foreign controlled studies with nifedipine capsules in which adverse reactions were reported spontaneously, adverse effects were frequent but generally not serious and rarely required discontinuation of therapy or dosage adjustment. Most were expected consequences of the vasodilator effects of Procardia. Adverse experiences reported in placebo-controlled trials include: dizziness, lightheadedness, and giddiness (27%, compared to 15% placebo incidence); flushing, heat sensation (25%, compared to 8% placebo incidence); headache (23%, compared to 20% placebo incidence); weakness (12%, compared to 10% placebo incidence); nausea, heartburn (11%, compared to 8% placebo incidence); muscle cramps, tremor (8%, compared to 3% placebo incidence); peripheral edema (7%, compared to 1% placebo incidence); nervousness, mood changes (7%, compared to 4% placebo incidence); palpitation (7%, compared to 5% placebo incidence); dyspnea, cough, and wheezing (6%, compared to 3% placebo incidence); and nasal congestion, sore throat (6%, compared to 8% placebo incidence).

There is also a large uncontrolled experience in over 2100 patients in the United States. Most of the patients had vasospastic or resistant angina pectoris, and about half had concomitant treatment with beta-adrenergic blocking agents. The relatively common adverse events were similar in nature to those seen with PROCARDIA XL.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

In a subgroup of over 1000 patients receiving Procardia with concomitant beta blocker therapy, the pattern and incidence of adverse experiences was not different from that of the entire group of Procardia treated patients (See PRECAUTIONS.)

In a subgroup of approximately 250 patients with a diagnosis of congestive heart failure as well as angina, dizziness or lightheadedness, peripheral edema, headache or flushing each occurred in one in eight patients. Hypotension occurred in about one in 20 patients. Syncope occurred in approximately one patient in 250. Myocardial infarction or symptoms of congestive heart failure each occurred in about one patient in 15. Atrial or ventricular dysrhythmias each occurred in about one patient in 150.

In post-marketing experience, there have been rare reports of exfoliative dermatitis caused by nifedipine.

More detailed professional information available on request.

Revised July 1990

Pfizer Labs

READERS' COMMENTS

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Assessing Left Ventricular Ejection Force

Association of Coronary Artery Disease in Cardiac Transplant Recipients with Cytomegalovirus Infection

Correction

INSTRUCTIONS TO AUTHORS on page 1024

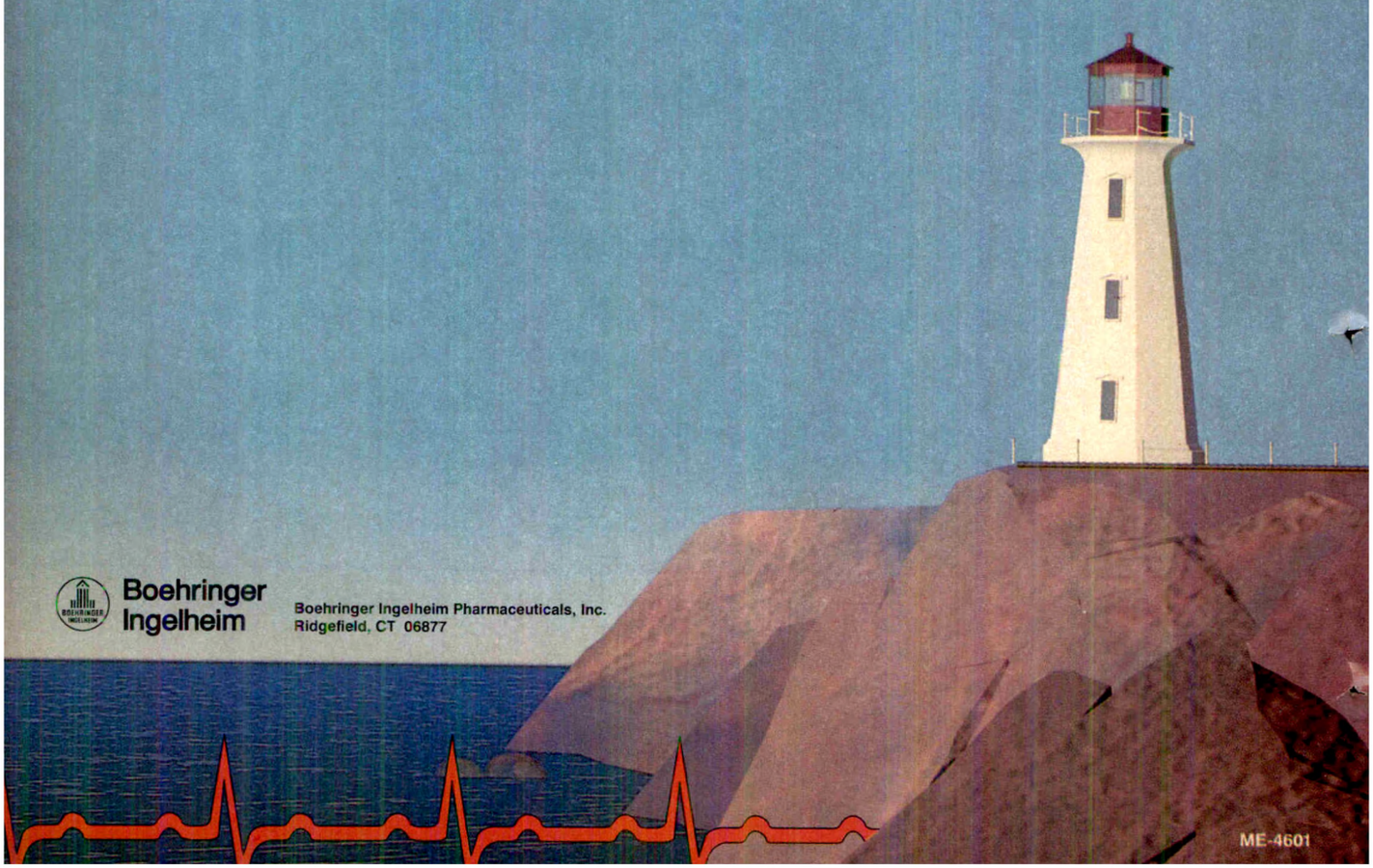
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The American Journal of Cardiology

OCTOBER 15, 1990, VOL. 66, NO. 12

Transient Left Ventricular Filling Abnormalities (Diastolic Stunning) After Acute Myocardial Infarction

Brian D. Williamson, MD, Michael J. Lim, BS, and Andrew J. Buda, MD

A variety of experimental studies suggest that diastolic left ventricular (LV) function changes after acute myocardial infarction (AMI), but limited data exist on these changes in humans. To assess diastolic filling after AMI, 60 patients underwent Doppler echocardiographic examination within 24 hours of AMI. Of 54 patients who also underwent catheterization, 45 (83%) were successfully reperfused. A subgroup of 17 patients underwent a follow-up Doppler examination at 7 days after infarction, whereas 15 patients with stable exertional angina served as control subjects. There was no significant difference in age, gender, incidence of systemic hypertension or diabetes mellitus, heart rate, mean arterial pressure or severity of coronary artery disease between the infarct and control groups. The infarct group had a lower velocity time integral total (9.9 ± 0.4 cm vs 12.0 ± 0.9 cm, p <0.001), a lower velocity time integral E (5.8 ± 0.3 cm vs 6.8 ± 0.5 cm, p <0.01) and a lower velocity time integral 0.333 (3.5 ± 0.4 cm vs 6.1 ± 0.5 cm, p <0.01) than the control group. In addition, velocity time integral A/total was significantly greater in the infarction group (0.44 ± 0.03 vs 0.35 ± 0.04, p <0.01) compared to the control group. The follow-up subgroup showed an increase in velocity time integral total (p <0.01), velocity time integral E (p <0.05) and velocity time integral 0.333/total (p <0.05) over the first 7 days after infarction. The final recovery values at 7 days were not significantly different from those of the coronary artery disease group. Patients with initial ejection fractions <40% or anterior infarction had the greatest recovery during the 7-day period. In conclusion, LV filling is further impaired during acute infarction compared to patients with stable coronary artery disease with the predominant impairment in early diastole. After infarction, filling parameters improve over the first 7 days after AMI, suggesting a recovery of diastolic stunning.

(Am J Cardiol 1990;66:897–903)

Acute myocardial infarction (AMI) is well known to produce impaired systolic function, whereas reperfusion may attenuate the measured decline in systolic function.[1,2] The concept of myocardial stunning has been proposed to explain the delayed recovery in systolic myocardial performance after AMI.[3] The impact of AMI and reperfusion on left ventricular (LV) diastolic performance and the possibility of diastolic stunning is less clear. In this regard, it has been shown that transient myocardial ischemia can result in diastolic filling abnormalities in addition to systolic dysfunction.[4,5] Furthermore, experimental studies have indicated that AMI leads to abnormal LV stiffness or relaxation that may improve with time.[6,7] The nature and extent of LV diastolic dysfunction in AMI in humans and its potential for recovery remain unsettled. The development of Doppler echocardiography has allowed the noninvasive measurement of diastolic filling, which correlates well with other measures of filling.[8] Accordingly, this study characterizes Doppler LV filling in patients with AMI compared to patients with stable coronary disease and determines if changes in filling occur during the first 7 days after AMI, which may support the existence of diastolic stunning.

METHODS

These studies were approved by the Human Subjects Review Committee of the University of Michigan Medical School and informed consent was obtained from each patient.

Study group: Pulsed Doppler echocardiograms were performed in 60 patients (51 men, 9 women) within 24 hours of admission with AMI as determined by typical history, standard electrocardiographic changes and an increase in cardiac enzymes. No patient had significant valvular heart disease, evidence of mitral regurgitation

From the Cardiology Division, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan. Michael Lim was supported by a Student Fellowship Grant from the American Heart Association of Michigan, Lathrup Village, Michigan. Manuscript received April 9, 1990; revised manuscript received and accepted June 4, 1990.

Address for reprints: Andrew J. Buda, MD, Cardiology Division, University of Michigan Medical Center, 1500 East Medical Center Drive, Taubman Ctr 3910L, Ann Arbor, Michigan 48109-0366.

TABLE I Demographics and Clinical Parameters for Patients in the Coronary Artery Disease Control Group, Patients in Acute Myocardial Infarction Group, and Patients in Follow-Up Subgroup

	CAD (n = 15)	MI (n = 60)	F/U (n = 17)	p Value
Age (mean)	56 ± 9	57 ± 10	58 ± 2	NS
Men	12 (80%)	52 (87%)	12 (71%)	NS
Hypertension	5 (33%)	31 (52%)	9 (53%)	NS
Diabetes mellitus	3 (20%)	14 (23%)	6 (35%)	NS
Extent of CAD				
1 vessel	9 (60%)	33 (55%)	10 (59%)	NS
2 vessels	6 (40%)	17 (28%)	6 (41%)	NS
3 vessels	0 (0%)	4 (7%)	1 (5%)	NS

CAD = coronary artery disease (defined as ≥70% narrowing of a major coronary artery or branch); F/U = follow-up subgroup, MI = acute myocardial infarction group; NS = not significant.

TABLE II Hemodynamics and Peak Filling Velocities for Patients in the Coronary Artery Disease Group and the Acute Myocardial Infarction Group

	CAD (n = 15)	MI (n = 60)	p Value
HR (beats/min)	66 ± 2	80 ± 3	NS
MAP (mm Hg)	79 ± 3	85 ± 2	NS
Peak E (cm/s)	56 ± 2	54 ± 2	NS
Peak A (cm/s)	51 ± 4	57 ± 2	NS
Peak E/A	1.1 ± 0.1	1.0 ± 0.1	NS

CAD = coronary artery disease group; HR = heart rate; MAP = mean arterial pressure; MI = acute myocardial infarction group; NS = not significant.

or cardiogenic shock and all were in a sinus rhythm and had a technically adequate study. Ejection fractions were determined in all patients within 24 hours of admission by radionuclide techniques.

The patients ranged in age from 37 to 76 years (mean 57). All patients developed new Q waves during hospitalization. Thirty-one had a history of systemic hypertension and 14 were known to have diabetes mellitus. Thirty-one patients had anterior AMI and 29 had inferior AMI.

Diagnostic catheterization was performed in 54 patients during the first week after infarction (6 patients refused catheterization). Thirty-three patients had 1-vessel disease (defined by a ≥70% narrowing of a major coronary artery or branch), 17 had 2-vessel and 4 had 3-vessel disease. Forty-five of these 54 patients (83%) were successfully reperfused, as determined by an open infarct-related vessel at catheterization.

A subgroup of 17 patients underwent a follow-up Doppler examination 7 days after admission as part of a later phase of patient recruitment. These patients ranged in age from 37 to 76 years (mean 56). Eight patients had inferior AMI while 9 patients had anterior AMI. Serial measurements of systolic function by radionuclide or contrast ventriculography were available in 14 of these patients. There was no difference in age, gender, blood pressure, severity of coronary artery disease, ejection fraction or Doppler filling parameters between these patients and the infarct group as a whole, as listed in Table I.

Control group: Doppler studies were also performed on 15 patients with angiographically documented coronary artery disease (12 men, 3 women). These patients ranged in age from 36 to 74 years (mean 56) and had a history of typical stable exertional angina, ≥70% narrowing of a major coronary artery or large branch, LV ejection fraction of 50% and no evidence of valve disease. No patient had previous myocardial infarction, as determined by history, electrocardiogram and wall motion analysis. Five patients had a history of systemic hypertension and 3 had diabetes mellitus. Nine patients had 1-vessel and 6 had 2-vessel disease.

Doppler studies: Pulsed-wave Doppler examinations of the LV inflow were performed with a 2.5-MHz transducer. Using the apical 4-chamber view, the Doppler sample volume (5 mm) was placed in the mitral valve funnel on the LV side of the mitral anulus. The sample volume was placed as parallel to flow as possible to maximize recorded velocity.[9] The tracings were recorded on a strip chart recorder at a paper speed of 100 mm/s.

A digitizing pad and a microcomputer were used to analyze the Doppler wave forms. Wave form analysis was performed by tracing the modal velocity (darkest portion) of each beat and averaging ≥3 consecutive beats.[10] Peak filling velocities of the early rapid filling wave (E) and the atrial contraction wave (A) as well as the E/A ratio were determined. Velocity time integrals, reflecting the area under the wave form, were computed for the total diastolic cycle (velocity time integral total), as well as for early filling (velocity time integral E), late atrial filling (velocity time integral A) and the first one-third of the diastolic cycle (velocity time integral 0.333).

Statistical analysis: All results are expressed as mean ± standard error of the mean. Comparisons were made between the filling parameters and hemodynamics of the infarct group and the coronary artery disease group. Paired comparisons were also made between the acute and follow-up studies in the 7-day follow-up subgroup. A 2-tailed Student's *t* test was used for all the analyses.

RESULTS

Comparison of initial filling after infarction to control subjects: The coronary artery disease control group was age- and sex-matched to the AMI group. There was no difference in incidence of diabetes mellitus, systemic hypertension or severity of coronary artery disease between the 2 groups as listed in Table I.

Heart rate and mean arterial pressure were not significantly different between groups. Peak early filling (E), late filling velocity (A) and E/A ratio did not differ significantly between the coronary artery disease and acute infarction groups (Table II). However, there were differences between the velocity time integrals in the infarct group and the coronary artery disease control subjects, as shown in Figure 1. There was a significantly lower total filling integral (velocity time integral total) in the infarct group (9.9 ± 0.4 cm vs 12.0 ± 0.9 cm, $p < 0.001$), as well as lower early diastolic filling (velocity time integral E; 5.8 ± 0.3 cm vs 6.8 ± 0.5 cm, $p < 0.01$), and first third velocity time integral (3.5 ±

TABLE III Twenty-Four-Hour Doppler Examination Parameters for Patients in the Acute Myocardial Infarction Group Compared to Patients in the Follow-Up Subgroup

	MI (n = 60)	F/U (n = 17)	p Value
Peak E (cm/s)	53 ± 2	5 ± 5	NS
Peak A (cm/s)	57 ± 2	55 ± 4	NS
Peak E/A	1.0 ± 0.1	0.9 ± 0.1	NS
VTI E (cm)	5.8 ± 0.3	5.1 ± 0.2	NS
VTI A (cm)	4.4 ± 0.2	4.2 ± 0.2	NS
VTI E/A	1.6 ± 0.1	1.4 ± 0.2	NS

VTI = velocity time integral; other abbreviations as in Table I.

TABLE IV Hemodynamics and Peak Filling Velocities for Patients in the Follow-Up Subgroup

	AMI (n = 17)	F/U (n = 17)	p Value
HR (beats/min)	82 ± 3	76 ± 2	NS
MAP (mm Hg)	85 ± 2	83 ± 2	NS
Peak E (cm/s)	50 ± 5	55 ± 3	NS
Peak A (cm/s)	55 ± 4	61 ± 4	NS
Peak E/A	0.9 ± 0.1	1.0 ± 0.1	NS

AMI = 24-hour study for follow-up subgroup; other abbreviations as in Table II.

0.4 cm vs 6.1 ± 0.5 cm, p <0.01). The proportion of the late filling to total filling, as measured by velocity time integral A/total, was significantly greater in the infarct group (0.44 ± 0.03 vs 0.35 ± 0.04, p <0.01), whereas velocity time integral E/total and velocity time integral E/A were not significantly different between the 2 groups.

Of the 54 infarction patients who underwent catheterization, 45 were successfully reperfused. There were no significant differences in peak velocities or velocity time integrals on the acute examinations based on whether reperfusion was successful.

Changes in filling during the first week after infarction: The subgroup of 17 patients with follow-up examinations did not differ significantly from the infarct group as a whole in the clinical parameters of age, gender, systemic hypertension, diabetes mellitus, heart rate, blood pressure or severity of coronary artery disease. Furthermore, the follow-up subgroup had similar Doppler indexes on the 24-hour examination compared to the AMI group as a whole (Table III). Heart rate, mean arterial pressure, peak E, peak A and peak E/A were not significantly changed over the first 7 days, as listed in Table IV. There were, however, significant changes in the velocity time integrals over this time.

Figure 2 shows the changes in mean velocity time integrals from the acute to the follow-up examination. The mean total velocity time integral was depressed acutely, but recovered by 1 week (8.5 ± 0.7 cm to 11.8 ± 1.1 cm; p <0.01) to that of control subjects. Similarly, early filling, as measured by velocity time integral 0.333, and velocity time integral E were depressed acutely (3.5 ± 0.4 cm and 5.1 ± 0.5 cm, respectively) and showed significant recovery after 7 days (5.2 ± 0.5 cm, p <0.01 and 6.8 ± 0.7 cm, p <0.05, respectively). Again, the follow-up values were not significantly different from coronary artery disease control subjects. There was no significant change in velocity time integral A from acute to follow-up examination.

Velocity time integral A/total was lower at follow-up than it was acutely (0.4 ± 0.02 vs 0.5 ± 0.04), although statistical significance was not quite reached (p = 0.07). Velocity time integral 0.333/total increased significantly from the initial study to 7 days (0.42 ± 0.04 vs 0.45 ± 0.03; p <0.05) but velocity time integral E/total was unchanged. The peak velocities and velocity time integrals at 7 days were not significantly different from those of the coronary disease control group.

Serial measurements of global systolic function by radionuclide or contrast ventriculography were available in 14 of the 17 patients in the follow-up subgroup. There were no significant changes in ejection fraction from the first to the seventh day after infarction (initial mean 43.1 ± 2.5% vs a follow-up mean of 45.4 ± 3.0%, p = 0.57).

Subgroup analysis was performed in the follow-up patients to compare anterior myocardial infarction versus inferior infarction and ejection fraction >40% vs

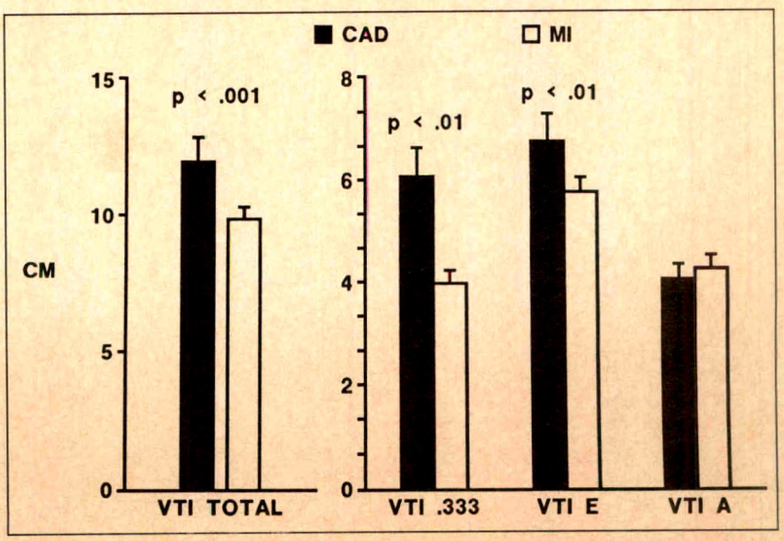


FIGURE 1. Comparison of velocity time integrals of total diastolic filling (velocity time integral total), first third of diastole (velocity time integral 0.333), early filling (velocity time integral E) and late filling (velocity time integral A) in coronary disease control subjects versus acute myocardial infarction group. CAD = coronary artery disease control group; CM = centimeters; MI = acute myocardial infarction group; VTI = velocity time integral.

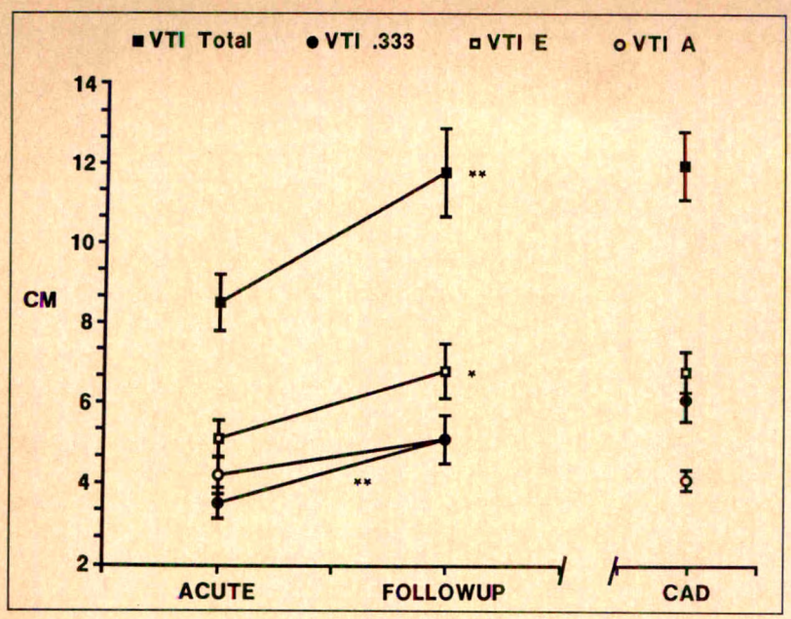


FIGURE 2. Velocity time integrals of total filling (velocity time integral total), first third diastole (velocity time integral 0.333), early filling (velocity time integral E) and late filling (velocity time integral A) at 24 hours and the 7 days after infarction. Values for the coronary artery disease control group are placed on right side of the graph for reference. *p <0.05 vs 24 hours; **p <0.01 vs 24 hours.

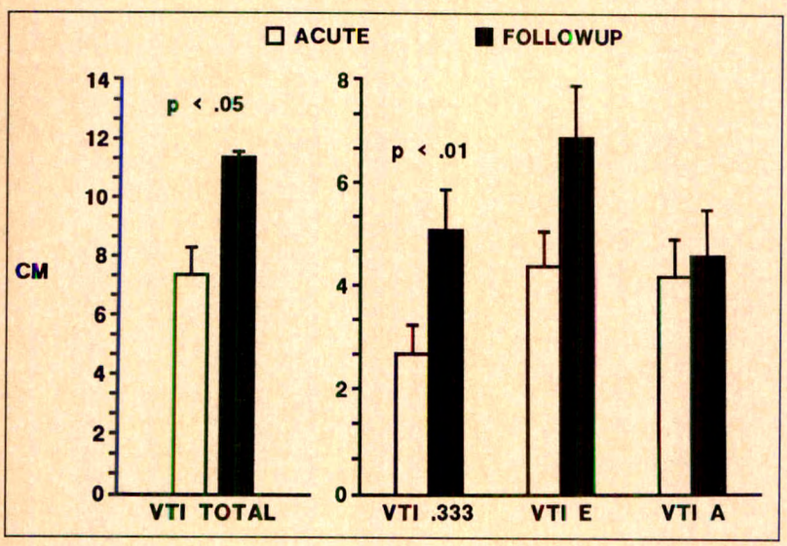


FIGURE 3. Comparison of velocity time integrals between acute and follow-up examinations in the subgroup of patients with anterior myocardial infarction.

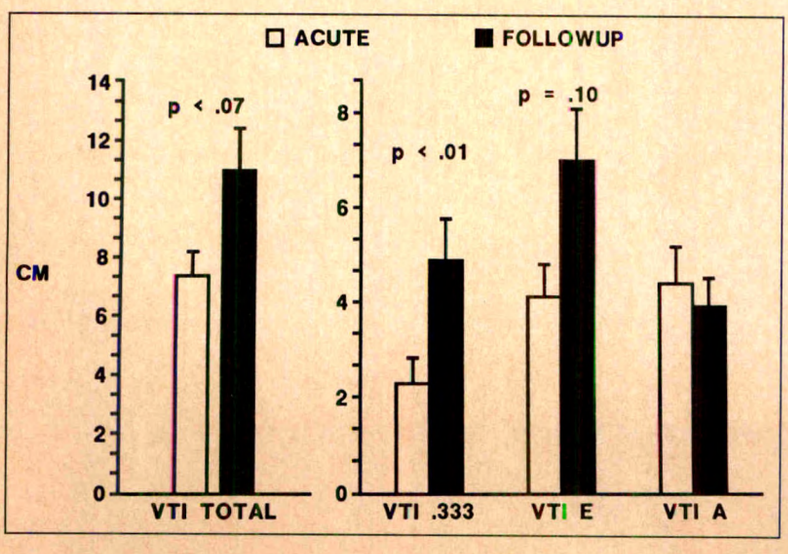


FIGURE 4. Velocity time integrals for the acute and follow-up examinations in patients with initial ejection fraction <40%.

<40%. There was no significant change in hemodynamics over the week after infarction in the group as a whole, although patients with anterior infarction had a statistically significant change in heart rate over the 7-day follow-up period (89 ± 4 vs 78 ± 3 beats/min respectively, p <0.01). There were no significant changes in peak filling velocities over time, but in patients with anterior infarction, a significant improvement in velocity time integral total (7.4 ± 0.9 cm vs 11.4 ± 1.6 cm, p <0.05) and velocity time integral 0.333 (2.7 ± 0.5 cm vs 5.1 ± 0.8 cm, p <0.01) was seen (Figure 3). The patients with inferior infarction did not show significant changes in peak velocities or velocity time integrals.

Similarly, in the subgroup of patients with initial ejection fraction <40%, there was no change in hemodynamics or peak filling velocities. However, despite the limited number of patients, a significant improvement in early filling as measured by velocity time integral 0.333 (2.4 ± 0.5 cm vs 5.1 ± 0.9 cm, p <0.01) was seen in this subgroup of patients with initially impaired ejection fraction. Velocity time integral total and velocity time integral E showed trends to increase within 7 days, but statistical significance was not quite reached. These results are shown in Figure 4. Patients with initial ejection fractions that were >40% did not show any significant changes in peak filling velocities or velocity time integrals over the first 7 days.

Sixteen of the 17 follow-up patients were successfully reperfused. Because of the high incidence of reperfusion in this group, subgroup analysis to compare filling parameters at follow-up based on reperfusion status was not possible.

DISCUSSION

Alterations in LV filling dynamics may be due to a variety of mechanisms, including changes in myocardial stiffness, impaired LV relaxation, changes in right ventricular loading conditions, pericardial constraints, viscoelastic considerations and nonuniformity, among others.[11] Clearly, the determinants of diastolic filling are complex. The aim of this study was not to set apart the impact of these various forces, but to measure LV filling after AMI and the changes that occur in filling over time, as a reflection of possible recovery.

The important new observations from our study are the following: early diastolic LV filling after AMI is decreased, while the atrial contribution to filling is maintained; filling is most impaired initially in patients with anterior infarction or with more severely depressed ejection fraction; and normalization of filling patterns occurs in the first week after AMI.

It is well known that myocardial ischemia can lead to impairment in systolic function, with regional wall motion abnormalities resulting in decreased ejection fraction and increased ventricular volumes.[12] The impact of acute ischemia on diastolic properties has been less well defined. Several investigators have observed an upward shift in the pressure-volume curve with myocardial ischemia as a result of an increase in resistance to LV filling or increased chamber stiffness.[13,14] These diastolic abnormalities during acute ischemia are further reflected by impairment in early LV filling after transient coronary occlusion by angioplasty.[4]

Diastolic filling in coronary artery disease: In addition to these findings with acute ischemia, a number of studies have identified abnormal filling patterns in patients with stable coronary artery disease. Radionuclide angiography has shown that patients with coronary artery disease have impaired early peak LV filling rates at rest, independent of systolic function or previous AMI. These filling abnormalities have been shown to normalize after revascularization, either by angioplasty or coronary bypass surgery.[15,16] Wind et al,[9] using Doppler echocardiography, showed significantly depressed peak E (early diastolic) velocity in patients with stable coronary artery disease and normal global systolic function as well as an increased percentage of the Doppler LV filling during late diastole. These diastolic LV filling abnormalities persisted 24 hours after successful angioplasty. Thus ischemia, in the absence of AMI, can lead to prolonged abnormalities in early filling, with preservation of late filling due to atrial systole. In this study, diastolic LV filling was equally impaired acutely in patients who had been successfully reperfused and in those who had not. Although this impairment may be reversible, the time course and mechanism of such recovery is not well known.

Diastolic LV filling abnormalities have also been reported in patients with remote AMI. Fuji et al[17] studied 40 patients with previous AMI and found prolonged deceleration and acceleration half-times of transmitral inflow, as well as an increase in late diastolic inflow relative to early filling, suggesting that weeks after AMI, early diastolic filling is impaired, which may be compensated for by atrial systole. Thus, these data, in combination with our own, may suggest that diastolic function initially is impaired after AMI, improves over the first 7 days, but then becomes further impaired as infarct healing and scarring occur. However, additional serial studies in patients after AMI will be necessary to support this hypothesis.

Other factors, such as hypertension, diabetes and mitral regurgitation, have been shown to affect filling dynamics. However, there was no difference in the incidence of these clinical parameters in the infarction patients and the control group.

Impact of reperfusion: The development of thrombolysis has provided the potential to change the natural history of AMI. The post-AMI period has been shown to result in dynamic changes with consequent myocardial remodeling and possible infarct expansion. The impact of thrombolysis and reperfusion on subsequent systolic and diastolic performance has only recently been addressed.[18,19] Global and regional systolic function may be preserved both in experimental animals and in humans after infarction with reperfusion.[20,21] However, little is known in humans concerning diastolic performance after acute ischemia and reperfusion. In this regard, our study provides new observations on changes in diastolic filling after reperfusion. Almost all patients in this study underwent successful reperfusion, which may have contributed to the improvement in filling dynamics

over time. The percentage of patients who did not have successful reperfusion was too small to assess the differential impact reperfusion had on diastolic filling in the recovery period.

Few experimental studies have addressed the effect of reperfusion on diastolic performance. Kurnik et al[6] examined the impact of AMI and reperfusion on myocardial and chamber stiffness in a canine model. They found coronary occlusion led to a decrease in LV systolic function and a concomitant increase in myocardial and chamber stiffness. One hour of occlusion with subsequent reperfusion resulted in improvement in systolic function and decreased stiffness by 1 week. On the other hand, late reperfusion or permanent occlusion resulted in persistent abnormalities in indexes of systolic and diastolic function. Tilton et al[7] examined LV segmental relaxation in dogs undergoing a 2- or 4-hour coronary occlusion followed by reperfusion. They found that the recovery of diastolic function occurred in the first week after AMI. Thus, the findings of this experimental study concur with our clinical observations, which showed an improvement in diastolic filling over the first week after AMI.

Potential mechanisms: The determinants of diastolic filling are complex and cannot be differentiated in our study. However, 2 major mechanisms of impaired filling in the setting of AMI are decreased myocardial relaxation and increased LV stiffness. Decreased relaxation would be expected to have its greatest impact during early diastole, as the transition from active contraction to active relaxation occurs.[22] Impaired relaxation after AMI appears to be due to depletion of adenosine triphosphate stores or changes in intracellular calcium concentration.[23–25] Increased stiffness, while it may affect the slope of the pressure-volume curve throughout diastole, would tend to provide the greatest resistance to filling near end-diastole, at maximum ventricular distention.[22] This increased stiffness may be secondary to edema formation early after AMI, or developing fibrosis in the late post-AMI course.[26] Both of these mechanisms may play a role in contributing to observed diastolic filling abnormalities.

In addition to decreased myocardial relaxation and increased LV stiffness, there are a number of other factors that may also play a role in diastolic filling abnormalities. These include the production of reactive oxygen metabolites, which have been shown to interfere with sarcoplasmic reticulum function, extrinsic factors such as pericardial constraints and right ventricular loading conditions, and temporal nonuniformity of relaxation. Clearly, further investigation will be necessary to delineate the contributions of these multiple factors.

Recent experimental models have shown that postischemic reperfused myocardium exhibits abnormalities in diastolic as well as systolic performance, which may be prolonged but which have the potential for recovery.[7,27] These findings have been proposed to reflect stunning of both systolic and diastolic properties (i.e., sublethal ischemic injury to myocardial cells results in functional abnormalities, which may be reversible once flow is restored). Our clinical findings are consistent with the hypothesis of stunning of diastolic function after ischemic injury with recovery after reperfusion.

The decrement in total filling observed in this study may also be related to changes in cardiac output, since concomitant changes in systolic performance occur after AMI.[27] However, the overall pattern of diastolic filling changed with infarction, with the predominate impact on filling occurring during early diastole, which normalized in the recovery period. This differential change in the pattern of LV filling suggests a concomitant abnormality in diastolic performance. Furthermore, the changes in diastolic filling that occurred during the first week after AMI were not accompanied by improvement in systolic function measured by ejection fraction. Thus, our study supports the concept that perturbations in systolic and diastolic function are tightly interrelated and that ischemia results in a global stunning of myocardial performance with gradual recovery after reperfusion.

Study limitations: Several studies have shown the effect preload can have on filling dynamics.[28,29] Decreased preload, such as by occlusion of the vena cava or by intravenous nitroglycerin decreases peak early filling, whereas increased preload via volume infusion augments early filling.[30] In general, one might expect higher filling pressures after infarction, which would have augmented early filling, which was the opposite of our findings. Thus, it seems unlikely that the changes we observed can be accounted for by changes in preload. However, since invasive hemodynamic correlates were not available in all of our patients, changes in preload affecting early diastolic filling cannot be excluded. Heart rate can also alter diastolic filling. Although there was a trend toward higher heart rates initially after AMI, it was not statistically significant. In the subgroup of patients with anterior AMI, heart rate significantly decreased within 1 week, although the AMI group as a whole, as well as other subgroups, did not have significant changes in heart rate with serial examinations. Thus, it is unlikely that the changes in filling that we observed can be explained by these other factors.

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Comparison of Coronary and Myocardial Morphologic Findings in Patients With and Without Thrombolytic Therapy During Fatal First Acute Myocardial Infarction

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The hearts of 61 patients (39 men aged 64 ± 11 years) who died from 5 hours to 42 days (median 3 days) after a fatal first acute myocardial infarction without having undergone percutaneous transluminal coronary angioplasty or coronary bypass surgery were studied to compare clinical and cardiac morphologic features of patients receiving thrombolytic therapy with tissue-plasminogen activator (t-PA) to those not receiving thrombolytic therapy. Comparison of findings in the 23 patients who received t-PA intravenously 3 ± 1 hours after onset of symptoms, with the 38 patients who did not, showed similar baseline characteristics with respect to: age, gender, history of hypertension; location of the infarct; heart weight; severity and numbers of coronary arteries narrowed; and frequencies of plaque rupture, plaque hemorrhage and coronary thrombi. Among the patients receiving t-PA, however, there was a greater frequency of platelet-rich (fibrin-poor) thrombi in the infarct-related coronary arteries (6 of 11 vs 4 of 25 thrombi; p = 0.02), more nonocclusive than occlusive thrombi (6 of 11 vs 4 of 25 thrombi; p = 0.02), and a lower frequency of myocardial rupture (left ventricular free wall or ventricular septum) (5 of 23 [22%] vs 18 of 38 [46%]; p = 0.045).

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Administration of thrombolytic agents early in the course of acute myocardial infarction often restores the patency of occluded coronary arteries,[1] improves left ventricular function[2–4] and improves survival.[5] Early reperfusion frequently converts "ischemic" to hemorrhagic infarcts.[6] The frequencies of myocardial rupture and cardiogenic shock, degrees of coronary luminal narrowing and frequency of plaque rupture are similar between patients with hemorrhagic and nonhemorrhagic infarcts.[6] The present study of 61 patients after a fatal first acute myocardial infarction compares the clinical and cardiac morphologic features of patients who received thrombolytic therapy with recombinant tissue-plasminogen activator (t-PA) to those who did not.

METHODS

No patient had a healed (previous) myocardial infarct at necropsy, and none had undergone coronary artery bypass surgery or percutaneous transluminal coronary angioplasty. Of the 61 patients, 23 received thrombolytic therapy with t-PA during the acute myocardial infarction as participants in the Thrombolysis in Myocardial Infarction (TIMI) studies. (For full details concerning criteria for inclusion into the TIMI studies see references 1, 7 and 8). The Pathology Branch, National Heart, Lung, and Blood Institute, served as the central pathology laboratory for the TIMI study. The hearts of 23 patients were submitted from 16 different centers participating in the TIMI trial (see Appendix). One of these 23 patients underwent cardiac transplantation 40 days after treatment and is still alive. The remaining 38 patients did not receive thrombolytic therapy and thus were not participants in the TIMI studies. The hearts of these 38 patients were submitted to the Pathology Branch from 14 different centers (see Appendix) between 1960 and 1986. The criteria for selection of these hearts were the same as for those of the TIMI participants—no patient had a previous (healed) myocardial infarct, no patient had coronary artery bypass surgery and none had angioplasty.

The hearts were fixed in 10% buffered formaldehyde for at least 3 days. The epicardial coronary arteries were excised intact and lightly decalcified by the formic acid-sodium citrate method[9] for approximately 12 hours. The arteries were sectioned transversely at 5-mm

intervals and the segments were labeled sequentially. All specimens were then dehydrated in ethanol and xylene and embedded in paraffin. One section (5 μ thick) from each 5-mm segment was stained by the Movat method[10] and another section from each 5-mm segment was stained with hematoxylin and eosin. The cardiac ventricles were cut transversely into slices approximately 1-cm thick from the apex to approximately 2-cm caudal to the posterior atrioventricular sulcus.

Luminal narrowing of the 4 major (left main, left anterior descending, left circumflex and the right) coronary arteries was determined by examination of histologic sections of each 5-mm segment. The degree of luminal narrowing for each segment was assessed by subdividing a circle, with the perimeter formed by the internal elastic lamina, into 4 equal quadrants.[11] These quadrants corresponded to the 4 degrees of reduction of luminal cross-sectional area—0 to 25, 26 to 50, 51 to 75 and 76 to 100%—with the latter being subdivided into 76 to 95 and 96 to 100%. In addition, a "coronary score" (of luminal narrowing) was calculated by assigning each of the 4 degrees of luminal narrowing a numerical value from 1 to 4. A 5-mm segment narrowed 0 to 25% in cross-sectional area had a score of 1, a segment narrowed 26 to 50%, a score of 2, and so forth. Each degree of narrowing was multiplied by the number of segments found to be narrowed by that degree. The sum for all 4 degrees of narrowing was then divided by the total number of segments studied for that artery, giving an overall coronary score from 0 to 4.

Plaque rupture was identified by a fissure within the atherosclerotic plaque that was associated with thrombus or hemorrhage into the plaque, with the defect in the plaque being continuous with the arterial lumen.

The amounts of fibrin, platelets and erythrocytes in thrombi were estimated microscopically on a 0 to 3+ scale (0 = none seen, 3+ = maximum seen). With observers not being aware of whether the patient received t-PA or did not, thrombi were estimated to be "platelet-rich" or "fibrin-rich" when the number of plusses scored for either component was greater than the number of plusses scored for the other.

Statistical comparisons of numerical data were performed by 2-tailed *t* tests (paired or unpaired as appropriate). Categorical data were compared by coded chi-square analysis. For these calculations the Stat View 512+ statistical package (Brain Power, Inc., Calabasas, California) was used in association with a Macintosh SE computer. All values reported are mean ± standard deviation.

RESULTS

Baseline characteristics: The 2 patient groups were quite similar; of the 61 patients with a fatal first acute myocardial infarct (39 men aged 64 ± 11 years), 23 received thrombolytic therapy with t-PA intravenously (doses as described previously[1,8,12]) within 3.1 ± 1.3 hours of onset of symptoms (Table I). Comparisons among patients receiving thrombolytic therapy with those who did not showed similar ages (62 ± 12 vs 65 ± 11 years; p = 0.22), gender (14 [61%] vs 25 [66%] men; p = 0.70), frequency of a history of systemic hypertension (14 of 23 [61%] vs 20 of 30 [67%]; p = 0.66), locations of the infarct (13 [57%] vs 22 [58%] posterior wall infarcts; p = 0.92), and heart weights by gender (men, 460 ± 100 g vs 479 ± 117 g, p = 0.60; women, 376 ± 84 g vs 408 ± 94 g, p = 0.42). The interval from chest pain to death for all 61 patients ranged from 5 hours to 42 days (mean 8 ± 11 days, median 3.2) with no significant difference between patients who received t-PA and those who did not (8 ± 12 days [median 2.0] vs 8 ± 9 days [median 4.2]; p = 0.88).

TABLE I Baseline Clinical Characteristics in 61 Patients With First Fatal Acute Myocardial Infarction With and Without Thrombolytic Therapy

	Thrombolytic Therapy		
	+ n = 23	0 n = 38	p Value
Age (years)	62 ± 12	65 ± 11	0.22
Men/women	14/9	25/13	0.70
Interval chest pain to rt-PA (hours)	3.1 ± 1.3	—	—
Death (days)	8 ± 12	8 ± 9	0.88
median	2.0	4.2	
History of hypertension	14	20 (n = 30)	0.66
Location of AMI [no. (%)]			
Anterior	9 (39)	16 (42)	0.82
Posterior	13 (57)	22 (58)	0.92
Lateral (only)	1 (4)	0	—
Right ventricle*	7 (30)	7 (18)	0.28
Heart weight (g)			
Men	460 ± 100	479 ± 117	0.60
Women	376 ± 84	408 ± 94	0.42
Dilated left ventricle [no. (%)]	11 (48)	15 (39)	0.52
Myocardial rupture [no. (%)]			
LVFW	2	11	
VS	3	7	
Total (%)	5 (22)	18 (47)	0.045

* Always associated with an infarct of the posterior wall of the left ventricle. Values are mean ± standard deviation.
AMI = acute myocardial infarction; LVFW = left ventricular free wall; VS = ventricular septum; + = yes, 0 = no.

Myocardial rupture: The frequency of myocardial rupture was lower among patients who received thrombolytic therapy than those who did not (5 of 23 [22%] vs 18 of 38 [47%]; p = 0.045). The frequency of myocardial rupture among the subset of 29 patients who died within 72 hours of the onset of chest pain was also lower in patients who received thrombolytic therapy than in those who did not (3 of 15 [20%] vs 9 of 14 [64%]; p = 0.02).

Left ventricular dilatation: Left ventricular dilatation, judged by visual inspection at necropsy, occurred in 26 of 61 patients (43%), with similar frequencies between patients with and without thrombolytic therapy (11 [48%] vs 15 [39%]; p = 0.52) and between patients with and without myocardial rupture (8 [35%] vs 18 [47%]; p = 0.34).

Coronary arterial narrowing: Of the 61 patients, 60 had narrowing >75% of the luminal cross-sectional area by atherosclerotic plaque alone in at least 1 of the 4 major epicardial arteries: 8 patients (13%) had only 1 artery so narrowed; 9 patients (15%), 2 arteries; and 43 (70%), 3 or 4 arteries so narrowed. Nine patients (15%)

TABLE II Degrees of Luminal Cross-Sectional Narrowing by Atherosclerotic Plaque in Patients With and Without Thrombolytic Therapy for First Fatal Acute Myocardial Infarction

Thrombolytic Therapy (no.)	Mean % (± SD) 5-mm Coronary Segments Narrowed by Various Degrees in Cross-Sectional Area by Plaque					Coronary Score (mean ± SD)	No. (mean ± SD) of 5-mm Segments
	0–25%	26–50%	51–75%	76–95%	96–100%		
Four Major Epicardial Arteries							
+ (23)	13 ± 12	22 ± 12	34 ± 11	27 ± 14	2 ± 4	2.78 ± 0.49	1,025 (45 ± 9)
0 (38)	11 ± 12	20 ± 13	35 ± 12	31 ± 15	3 ± 4	2.90 ± 0.40	1,756 (46 ± 11)
p Value	0.55	0.68	0.92	0.36	0.88	0.32	
Infarct-Related Artery							
+	9 ± 17	18 ± 14	40 ± 18	32 ± 21	2 ± 4	2.97 ± 0.55	420 (18 ± 6)
0	9 ± 14	17 ± 14	33 ± 9	38 ± 22	2 ± 5	3.07 ± 0.51	647 (17 ± 8)
p Value	0.95	0.90	0.16	0.25	0.48	0.49	

SD = standard deviation; + = yes; 0 = no.

had severe narrowing of the left main coronary artery (>75%). The infarct-related arteries were narrowed >75% by plaque at some point in 59 of 61 patients (97%). Comparison between patients who received thrombolytic therapy and those who did not showed similar percentages with 3 or 4 arteries so narrowed (15 of 23 [65%] vs 28 of 38 [74%], p = 0.48) and similar percentages of patients with infarct-related arteries narrowed >75% by plaque at some point (21 of 23 [91%] vs 37 of 38 [97%], p = 0.99). Similar percentages of coronary segments narrowed to the 5 degrees (0 to 25, 26 to 50, 51 to 75, 76 to 95 and 96 to 100%) by atherosclerotic plaque were found in patients who had and who had not received thrombolytic therapy (Table II). The overall coronary score of luminal narrowing was similar between the 2 groups for all 4 major epicardial coronary arteries together (2.8 ± 0.5 vs 2.9 ± 0.4, p = 0.32) and for the infarct-related arteries analyzed independently (3.0 ± 0.6 vs 3.1 ± 0.5, p = 0.49).

Coronary thrombus: Coronary thrombi were found in the infarct-related artery at necropsy in 36 of the 61 patients (59%) (Figure 1). Of these 36 patients with thrombi at necropsy, 2 were among the 10 patients (20%) who died within 24 hours of the onset of chest pain, 13 were among the 19 (68%) patients who died between 24 and 72 hours, and 19 were among the 29 (66%) who died >72 hours after the onset of chest pain. The frequencies of thrombi among all patients who died within 72 hours compared with the frequencies in those who died >72 hours from onset of symptoms were similar between those who received thrombolytic therapy and those who did not. The frequencies of thrombi were similar between all patients who received thrombolytic therapy and those who did not (11 of 23 [48%] vs 25 of 38 [66%], p = 0.17) (Table III). However, the number of nonocclusive thrombi was greater in patients who had received thrombolytic therapy than in those who had not (nonocclusive thrombi: 6 of 11 [55%] vs 4 of 25 [16%] thrombi; p = 0.02).

A greater frequency of platelet-rich thrombi in the infarct-related coronary arteries was found in patients who received thrombolytic therapy than those who did not (6 of 11 [55%] vs 4 of 25 [16%]; p = 0.02), with a lower frequency of fibrin-rich thrombi in the group receiving thrombolytic therapy (3 of 11 [27%] vs 19 of 25 [76%], p = 0.006) (Table III).

Plaque rupture and plaque hemorrhage: Rupture of an atherosclerotic plaque was present in the infarct-related coronary artery in 37 of the 61 hearts (61%) (Table III), and an additional 3 patients (40 [66%]) had plaque rupture involving a non-infarct-related artery (Figure 1). The plaque rupture occurred at sites of pultaceous debris (pale-staining areas rich in extracellular lipid consisting of amorphous gruel with numerous cholesterol clefts and variable amounts of inflammatory and foam cell infiltrates) in all but 2 patients. Plaque rupture was found in 26 (72%) of the 36 sites of thrombi, and was associated with hemorrhage into the plaque in 34 (92%) of the 37 cases of plaque rupture. Hemorrhage into an atherosclerotic plaque was present at some point in the infarct-related artery in 45 (74%) of the 61 patients and in a non-infarct-related artery in an additional 4 patients (49 [80%]); it occurred at 27 (75%) of the 36 sites of thrombus formation.

The frequency of plaque rupture was similar between patients who received thrombolytic therapy and those who did not, whether the infarct-related arteries were considered independently (17 [74%] vs 20 [53%], p = 0.10) or all 4 major epicardial coronary arteries were considered together (17 [74%] vs 23 [61%], p = 0.29). The frequency of plaque hemorrhage was also similar between the 2 groups (the 4 major epicardial arteries, 19 [83%] vs 30 [79%], p = 0.73; the infarct-related arteries, 19 [83%] vs 26 [68%], p = 0.22).

Plaque rupture by itself resulted in total or near-total obstruction of the infarct-related artery in only 2 of the 23 patients who received thrombolytic therapy and in 2 of the 38 patients who did not receive t-PA. Of the

TABLE III Frequency of Luminal Thrombi, Plaque Rupture and Plaque Hemorrhage in the Infarct-Related Arteries of Patients With and Without Thrombolytic Therapy for First Fatal Acute Myocardial Infarction

Thrombolytic Therapy (no.)	Coronary Thrombus: Total No. (%) of Pts.	Coronary Thrombus: Occlusive No. (% of total)	Composition: Platelet-Rich (no. [%])	Composition: Fibrin-Rich (no. [%])	Plaque Rupture (no. [%] pts.)	Hemorrhage into Plaque (no. [%] of pts.)
+ (23)	11 (48)	5 (45)	6 (55)	3 (27)	17 (74)	19 (83)
0 (38)	25 (66)	21 (84)	4 (16)	19 (76)	20 (53)	26 (68)
p Value	0.17	0.02	0.02	0.006	0.10	0.22

Abbreviations as in Table II.

TABLE IV Degrees of Luminal Cross-Sectional Area Narrowing at Sites of Plaque

Thrombolytic Therapy	No. of S PR	No. (%) of S Narrowed in CSA by Plaque at Sites of PR: 0–25%	25–50%	51–75%	76–95%	96–100%
+	42	0	1 (2)	10 (24)	29 (69)	2 (5)
0	59	0	2 (3)	17 (29)	37 (63)	3 (5)
Total	101	0	3 (3)	27 (27)	66 (65)	5 (5)

CSA = cross-sectional area; PR = plaque rupture; S = segments; + = yes; 0 = no.

total of 101 five-mm coronary segments with plaque rupture (from the 37 patients with plaque rupture), the lumen was narrowed 51 to 75% in cross-sectional area by plaque in 27 segments (27%); 76 to 95% in 66 segments (65%); and 96 to 100% in 5 segments (5%) (Figure 1). Similar degrees of narrowing at sites of plaque rupture were noted between patients who received thrombolytic therapy and those who did not (Table IV).

The mean percentages of all 5-mm segments of the 4 major coronary arteries with plaque rupture and plaque hemorrhage are listed in Table V. This analysis of the 46 ± 11 five-mm coronary segments from each of the 61 patients (total = 2,781 segments including 17 ± 8 segments from each infarct-related artery alone) disclosed similar frequencies of these structural features between patients who did and did not receive t-PA.

DISCUSSION

We studied the hearts of 61 patients who died shortly (mean 8 ± 11 days) after a first acute myocardial infarction: 23 of these had received intravenous thrombolytic therapy with t-PA an average of 3 ± 1 hours after the onset of chest pain, and 38 had not. Myocardial rupture (left ventricular free wall or ventricular septum) occurred in 38% of these 61 patients. An earlier study from this laboratory of patients dying during

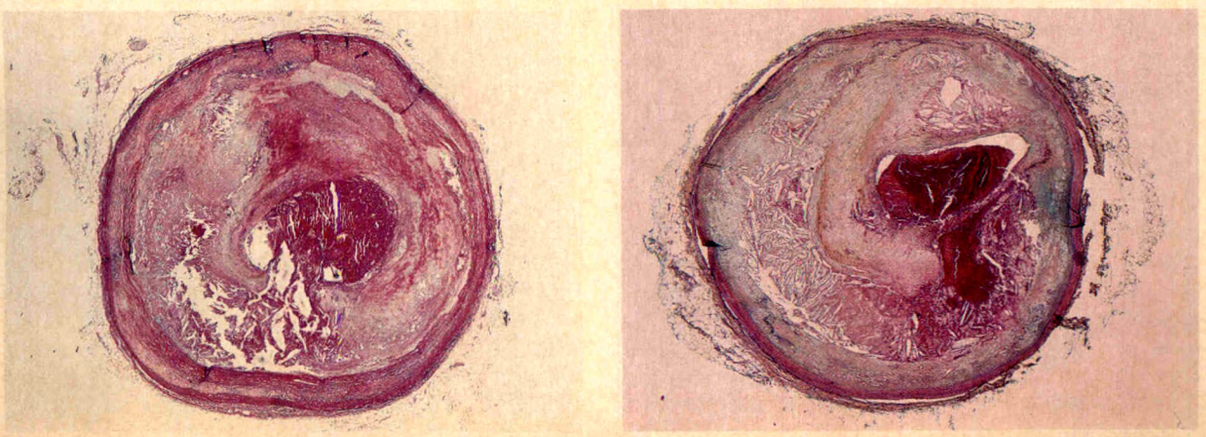


FIGURE 1. Rupture of atherosclerotic plaque in the infarct-related coronary artery of patients with first fatal acute myocardial infarction who did not receive thrombolytic therapy showing occlusion of the residual lumen by thrombus at sites of exposed pultaceous debris. By visual inspection, both lumens are narrowed 76 to 95% in cross-sectional area by atherosclerotic plaque alone. Right coronary artery *(left)* and left anterior descending coronary artery *(right)*. (Movat stains: × 15 *(left)*, × 20 *(right)*, reduced by 30%.)

TABLE V Mean Percent (± SD) of All 5-mm Segments with Plaque Rupture and Hemorrhage into a Plaque: Relation to Thrombolytic Therapy and to Interval from Chest Pain to Death

	IRA (no. of S = 1,067)		4 MEA (no. of S = 2,781)	
	PR	HIP	PR	HIP
Relation to Thrombolytic Therapy				
Thrombolytic therapy				
+	10 ± 9	17 ± 15	7 ± 7	9 ± 8
0	12 ± 16	15 ± 12	8 ± 10	7 ± 6
p Value	0.52	0.76	0.60	0.25
Relation to Interval from Chest Pain to Death				
>72 hours	14 ± 16	18 ± 23	8 ± 8	7 ± 6
<72 hours	9 ± 10	14 ± 15	7 ± 9	8 ± 7
p Value	0.20	0.43	0.55	0.50

HIP = hemorrhage into a plaque; IRA = infarct-related artery; MEA = major epicardial coronary arteries; SD = standard deviation. Other abbreviations as in Table IV.

acute myocardial infarction disclosed a higher frequency of myocardial rupture among those without a previous myocardial infarct (40%) compared to those with a previous (healed) infarct (13%),[13] and none of the patients included in the present study had a healed myocardial infarct. There has been concern that thrombolytic therapy might increase the frequency of rupture of the left ventricular free wall or ventricular septum during acute myocardial infarction. In the International Study of Infarct Survival-2 study, the frequency of myocardial rupture among all vascular deaths was apparently higher in patients treated with streptokinase within 24 hours of onset of chest pain than in those receiving placebo.[14] However, other studies have shown similar frequencies of cardiac rupture between patients who received thrombolytic therapy and control groups.[15,16]

The 61 patients comprising the present study died shortly after having their first myocardial infarction; thus, the frequency of rupture was expected to be, and indeed was, higher than in unselected patients dying of acute myocardial infarction. The frequency of myocardial rupture, however, was less in patients who received thrombolytic therapy (22%) than in those who did not (47%). This lower frequency of myocardial rupture in patients who received thrombolytic therapy was even more marked among those who died within 72 hours of onset of chest pain. One can argue that the higher frequency of myocardial rupture among our 38 patients who did not receive thrombolytic therapy might be due, in part, to selection bias from the 14 submitting centers. This laboratory, however, has received all or nearly all of the "cardiac cases" from 9 of these centers for many years accounting for 31, or 82%, of these cases. These results show that, even when considering the possibility of such bias, the previously feared increase in cardiac rupture in patients receiving thrombolytic therapy has not been confirmed.

The frequency at necropsy of thrombi in the infarct-related arteries of these patients with a fatal first acute myocardial infarction was not significantly lower in patients who received thrombolytic therapy than in those who did not. This finding does not imply that thrombolytic therapy fails to lyse coronary thrombi since our observations were limited to patients who died. Moreover, the frequency of occlusive thrombi was significantly lower in the t-PA–treated group, and this difference persisted when the analysis was restricted to patients who died within 72 hours of onset of chest pain. The greater frequency of platelet-rich, and lower frequency of fibrin-rich, thrombi in patients who had received t-PA supports suggestions that residual or recurrent thrombi in such patients are thrombolytic-resistant platelet-rich thrombi which might require treatment with an antiplatelet agent.[17]

Rupture of an atherosclerotic plaque was found at some point in the infarct-related artery in 61% of the total 61 patients and in 51% of patients who died >72 hours from the onset of chest pain. Similar frequencies of plaque rupture, and its usually associated hemorrhage, were found between patients who received thrombolytic therapy and those who did not. A number of angiographic and necropsy studies have suggested a direct pathogenetic relation between rupture of an atherosclerotic plaque, coronary thrombus formation and acute myocardial infarction.[18–24] In the present study, plaque rupture usually occurred at sites of pultaceous debris formation. The association of plaque rupture with sites of extensive lipid-rich pultaceous debris also has been emphasized by others.[25–28] Rupture of the atherosclerotic plaque, however, was found to be responsible itself for total or near-total obstruction of the infarct-related artery, resulting in 96 to 100% reduction in luminal cross-sectional area, in only 4 of the 37 patients with plaque rupture. In most patients with plaque rupture, it was the associated thrombus that appeared to account for the total, or almost total, luminal obstruction.

Recent angiographic studies have suggested that the degree of stenosis of infarct-related coronary arteries is not a reliable predictor of the time or location of future myocardial infarction, and that infarction frequently develops in association with infarct-related arteries that previously were not severely narrowed.[29,30] We found the lumen to be narrowed by <75% in cross-sectional area (<50% diameter reduction) in 30% of segments with plaque rupture—a finding that supports the concept that even moderately obstructing atherosclerotic plaques may rupture and be responsible for the patients' death, but this appears to be responsible in only a minority of such patients. In 65% of the segments with plaque rupture, the cross-sectional area narrowing ranged from 76 to 95%. Thrombolytic therapy would still be expected to be of value in most patients with plaque rupture (and nonresistant thrombi), and the fact that intravenous administration of t-PA is known to result in the restoration of vascular patency in approximately 75% of patients[1,7,8] does not exclude plaque rupture as an integral pathogenetic step in the evolution of acute myocardial infarction. However, even after successful thrombolysis, plaque rupture, with its associated exposed thrombogenic stimuli, remains a predisposing

factor for thrombotic reocclusion, and this threat persists even after 72 hours.

The present study of hearts of patients dying a median of 2 to 4 days after their first myocardial infarction shows that those who received intraveous t-PA 3 ± 1 hours after onset of symptoms (compared to those with similar baseline characteristics who did not receive thrombolytic therapy) had greater frequencies of nonocclusive and platelet-rich (fibrin-poor) thrombi and a lower frequency of myocardial rupture.

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APPENDIX

List of Submitting Medical Centers (TIMI Patients): Baystate Medical Center, Springfield, MA; Baylor College of Medicine, Houston, TX (Ben Taub General Hospital and Methodist Hospital); Boston University, Boston, MA (Boston University Hospital and Boston City Hospital); Columbia University, New York, NY (Columbia Presbyterian Medical Center); Cornell Medical Center, New York, NY (New York Hospital); George Washington University Hospital, Washington, DC; Harvard University, Beth Israel Hospital, Boston, MA; Mayo Clinic and Foundation, Rochester, MN; New York Medical College, Valhalla, NY (United Hospital); Northwestern University, Chicago, IL (Evanston, Hospital); University of Alabama at Birmingham, Birmingham, AL (Carraway Methodist Medical Center); University of Massachusetts Medical Center, Worcester, MA; Yeshiva University, Albert Einstein College of Medicine, New York, NY (New Rochelle Hospital).

Non–TIMI Patients: National Institutes of Health, National Heart, Lung, and Blood Institute, Bethesda, MD; District of Columbia Medical Examiners Office, Washington, DC; District of Columbia Veterans Administration Hospital, Washington, DC; National Naval Medical Center, Bethesda, MD; George Washington University Medical Center, Washington, DC; Georgetown University Medical Center, Washington, DC; Suburban Hospital, Bethesda, MD; Emory University Hospital, Atlanta, GA; Washington Adventist Hospital, Takoma Park, MD; Franklin Square Hospital, Baltimore, MD; Mt. Sinai Medical Center, Miami Beach, FL; St. Vincent Health Center, Erie, PA; Hollywood Presbyterian Medical Center, Los Angeles, CA; Prince William Hospital, Manassas, VA.

Recombinant Tissue-Type Plasminogen Activator Followed by Heparin Compared with Heparin Alone for Refractory Unstable Angina Pectoris

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Patients with unstable angina pectoris who remain symptomatic despite medical treatment are at high risk of death and myocardial infarction. The incidence of refractory unstable angina was examined in a consecutive series of 103 patients who received conventional medical treatment with nitrates, β blockers, calcium antagonists and aspirin. During 48 hours of continuous electrocardiographic monitoring, 24 patients had ≥1 anginal attack, 5 of whom had both painful and painless ischemic episodes. In these 24 patients with unstable angina refractory to conventional medical treatment, the short-term efficacy of recombinant tissue-type plasminogen activator (rt-PA) followed by heparin was assessed and compared with heparin alone in a randomized double-blind trial. Recurrences of ischemic attacks during a 72-hour follow-up period were documented in 9 of the 12 patients given heparin alone. All patients experienced at least 1 symptomatic ischemic episode and 1 patient had both painful and painless ischemia. No patient given rt-PA plus heparin had either symptomatic or asymptomatic ischemic attacks during follow-up. Kaplan-Meier curves analysis demonstrated a significantly higher probability of being ischemia free in the group of patients treated with rt-PA followed by heparin than in the group treated with heparin alone ($p < 0.01$). Quantitative coronary arteriography failed to reveal any significant changes of ischemia-related lesions before and after each treatment. This study demonstrates that the combination of rt-PA and heparin has a greater protective effect than heparin alone in treating recurrent ischemic episodes in patients with refractory unstable angina. The clinical benefit of thrombolysis is not persistent and it does not eliminate the need for revascularization but may allow the procedures to be performed under more stable clinical conditions.

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Pharmacologic treatment of unstable angina has been directed at reducing oxygen demand, increasing coronary vasodilation and more recently inhibiting platelet aggregation. Although the condition of most patients will stabilize with hospitalization and with a combination of drugs administered in optimal doses, a subgroup of patients will continue to have ischemic attacks.[1–4] Previous studies have indicated that high rates of mortality and cardiac events occur in this subset of patients.[1,5,6] Emergency revascularization by coronary bypass graft surgery or by percutaneous transluminal coronary angioplasty is therefore often required.[5–8] Clinical approaches and technical improvements such as serial coronary arteriography,[9] high resolution fiberoptic angioscopy,[10] histopathologic and histochemical studies[11,12] have emphasized the importance of the process of plaque complication and thrombus formation in the pathophysiology of unstable angina. Recent studies have suggested that early heparin[13–15] and thrombolytic therapy may be useful in treating unstable angina.[16,17] The present study was designed to evaluate, in a highly selected group of patients with refractory unstable angina, whether the addition of single chain recombinant tissue-type plasminogen activator (rt-PA) and heparin compared with heparin alone may improve the short-term outcome. The angiographic characteristics of the ischemia-related lesions and their changes in morphology and severity were also evaluated after each treatment.

METHODS

Patients: We studied 103 consecutive patients admitted to our institution with a clinical diagnosis of unstable angina. The diagnosis was made independently by 2 experienced cardiologists and was defined as: (1) chest pain of recent onset, and (2) sudden worsening of preexisting stable angina or postinfarction angina developing after an asymptomatic period of >12 weeks and classified as Canadian Cardiovascular Society functional class III and IV. Prerequisite for the inclusion in the study was the occurrence of chest pain at rest associated with transient repolarization changes (ST-segment depression or elevation of ≥1 mm measured 80 ms after the J point or pseudonormalization of previously negative T waves). All patients who entered the study gave informed consent and the study protocol was approved by institutional committees.

Exclusions: Patients with the following conditions were excluded from the study: (1) age >75 years (24

patients), (2) persistent ST-T changes or elevation of creatine kinase greater than twice normal after episodes of chest pain (11 patients), (3) concomitant valvular heart disease (2 patients), (4) status of postcoronary artery bypass surgery (19 patients), (5) occurrence of Q-wave myocardial infarction within the previous 6 months (21 patients), and (6) refusal to participate in the study (3 patients). Patients with a contraindication to the use of thrombolytic therapy such as hematologic disorders (2 patients), recent history of bleeding (7 patients), recent surgery (1 patient), recent cerebrovascular accident (6 patients) and those with no significant coronary artery disease (3 patients) were also excluded from the protocol.

Conventional medical therapy: Conventional medical therapy was standardized by administering a combination of metoprolol, nifedipine, long-acting nitrates or intravenous nitroglycerin. If the use of metoprolol was contraindicated, diltiazem was administered in association with long-acting nitrates. Antiplatelet therapy was left to the discretion of the attending physician. Sedatives were used as needed. None of the patients were receiving heparin or oral anticoagulants before randomization. Continuous 2-lead Holter monitoring was performed for 48 hours from the time of entry into the study. The lead showing the most evident electrocardiographic changes during the ischemic attacks was monitored. The recorders were amplitude-modulated reel-to-reel 2-channel Holter monitor units (Delmar Avionics model 445), which were calibrated before and after placement for each 24-hour period. Tapes were analyzed usually at 60 times real time, and an episode of transient ischemia was defined as horizontal ST-segment depression or elevation of ≥1 mm for ≥80 ms after J point lasting ≥1 minute. A normal interval of ≥2 minutes was required after the resolution of each episode before another discrete episode was counted. Failure of conventional medical therapy was considered to have occurred in the event of persistent symptomatic or asymptomatic ischemic attacks at rest (at least 1 objectively documented by transient electrocardiographic changes or by ST-segment shift during Holter monitoring) during the 48-hour monitoring period.

Study protocol: At the end of the 48-hour monitoring period, the 24 patients who were unable to respond to conventional medical treatment were randomized in a double-blind manner to receive the addition of either placebo or rt-PA, 100 mg intravenously, both followed by heparin 5,000 IU intravenously every 6 hours. All patients continued to receive conventional medical treatment. The dose of rt-PA was administered as follows: 10 mg as a bolus administration followed by 50 mg within 1 hour and 40 mg over the next 4 hours (10 mg/hour). After completion of the 5-hour infusion period all patients were continuously monitored for recurrence of chest pain for 72 hours and Holter monitoring was performed at least for the first 24 hours. Only the 5 patients who had silent ischemic episodes during the 48-hour observation period underwent complete 72-hour Holter monitoring. Heparin was given to all patients starting immediately at the end of the infusion of rt-PA or placebo. During the 72-hour follow-up period, in which heparin was continuously given, activated partial thromboplastin time (APTT) was measured conventionally 4 hours after each bolus. When necessary, additional boluses of heparin were administered in order to maintain the APTT 1.5 to 2.0 times normal. The primary end point of the study was the failure of medical treatment, defined as the occurrence of either symptomatic or asymptomatic ischemic events (at least 1 objectively documented by transient electrocardiographic changes or by ST-segment shift during Holter monitoring) during the 72-hour follow-up period. All patients in this protocol were followed up until they were discharged or until another procedure such as angioplasty or coronary bypass surgery was performed.

Coronary arteriography: During the 48-hour observation period all 103 patients underwent selective coronary arteriography by standard Sones or Judkins technique. When a lesion was noted, the vessel was filmed again in multiple views after administration of nitroglycerin. Stenosis with a ≥75% diameter reduction persisting after nitroglycerin administration was considered significant. Left main coronary artery stenosis ≥50% was considered significant. In patients refractory to conventional medical treatment, coronary arteriography was repeated after the 72-hour follow-up period. The coronary artery supplying the ischemic zone was identified by reference to the electrocardiographic location of reversible ST-segment changes during chest pain. Qualitative morphologic analysis of the lesion of the ischemia-related artery was performed using the method of Ambrose et al[18] by 2 experienced cardiologists who were blind with respect to the response to conventional medical treatment. In addition to lesion classification, an attempt was made to identify intracoronary thrombi defined as spherical ovoid or irregular intraluminal filling defects surrounded on at least 3 sides by contrast medium just distal to or within a coronary stenosis.[19] The severity of an ischemia-related lesion before and after each treatment was quantitatively evaluated with the help of the computer-based system for coronary angiography analysis.

Data analysis: Continuous variables were analyzed with paired and unpaired *t* test of significance as appropriate. Categorical data were evaluated with chi-square test. We considered the time-dependent nature of treatment failure by applying the Kaplan-Meier actuarial method to examine failure rates over the time according to an intention-to-treat analysis. The Kaplan-Meir actuarial curves were then compared by a log-rank test using a 2-tailed significant level. Data are presented as mean ± standard deviation.

RESULTS

Patients refractory to conventional medical treatment: Seventy-nine patients had neither chest pain nor electrocardiographic evidence of ischemia under conventional medical treatment during the 48-monitoring hours (group I). The remaining 24 patients (group II) experienced at least 1 symptomatic ischemic episode; 5 of them also had silent ischemic attacks detected by Holter monitoring. There was no significant difference between groups I and II with regard to clinical and an-

TABLE I Clinical and Angiographic Characteristics of Patients with Unstable Angina Stabilized with Conventional Medical Treatment (Group I) and Refractory to Conventional Medical Treatment (Group II)

Characteristics*	Group I (n = 79)	Group II (n = 24)
Age (yrs)	58 ± 7	60 ± 10
Male (%)	56 (71)	18 (75)
History of hypertension		
No. of patients (%)	33 (42)	6 (25)
Duration of unstable angina (days)	24 ± 25	19 ± 24
Time between inclusion and last ECG-documented anginal episode (hours)	8 ± 13	8 ± 8
Prior myocardial infarction		
No. of patients (%)	28 (35)	9 (37)
ECG-documented left ventricular hypertrophy		
No. of patients (%)	17 (22)	3 (13)
ECG changes with pain		
No. of pts. (%)		
ST elevation	18 (23)	6 (25)
ST depression	61 (77)	18 (75)
Antianginal therapy		
No., % of treated patients and daily dose		
Metroprolol	39 (49)	13 (54)
	141 ± 50	138 ± 58
Nifedipine	36 (45)	12 (50)
	62 ± 19	63 ± 18
Long-acting nitrates	57 (72)	13 (54)
	99 ± 26	91 ± 33
Diltiazem	41 (52)	11 (46)
	307 ± 83	294 ± 91
Nitroglycerin (i.v.)	10 (12)	5 (20)
Aspirin	23 (29)	8 (33)
No. of diseased vessels		
No. of patients (%)		
0	3 (5)	0 (0)
1	28 (35)	9 (37)
2	28 (35)	7 (29)
3	20 (25)	8 (34)
Left main stenosis	4 (5)	1 (4)
No. of patients (%)		
Ischemia-related lesions morphology		
No. of patients (%)		
Concentric	28 (37)	8 (34)
Type I eccentric	18 (24)	4 (16)
Type II eccentric	17 (22)	5 (21)
Multiple irregularities	9 (12)	5 (21)
Total occlusion	4 (5)	2 (8)
Ischemia-related vessel intracoronary thrombus		
No. of patients (%)	11 (14)	4 (16)

* There was no significant difference between the 2 groups for any of these characteristics.

giographic characteristics (Table I). Among the 24 patients refractory to conventional management, 12 received heparin alone and 11 rt-PA plus heparin. One patient allocated to combined treatment did not receive it because of the development of persistent ischemia just before rt-PA infusion was started. This patient, who required emergency angioplasty, was included in the intention-to-treat analysis. During the 48-hour monitoring period, 43 ischemic episodes (38 symptomatic, 5 asymptomatic, total duration of ischemia 492 minutes) were observed in the group receiving rt-PA plus heparin and 103 ischemic episodes (30 symptomatic, 73 asymptomatic, total duration of ischemia 615 minutes) were observed in the group receiving heparin alone.

Short-term effect of recombinant tissue-type plasminogen activator plus heparin or heparin alone: Two patients treated with rt-PA plus heparin did not complete the 72-hour follow-up period because heparin was discontinued owing to bleeding complications. However, the outcomes in these 2 patients were recorded and included in the analysis. The rt-PA-plus-heparin group underwent Holter monitoring for a mean period of 38 ± 16 hours. All the patients treated with heparin alone completed the 72-hour follow-up and underwent Holter monitoring for a mean period of 36 ± 18 hours. During the follow-up period, 9 patients treated with heparin alone had recurrent ischemic episodes compared with none of the 11 patients receiving the combined treatment. A total of 22 ischemic episodes (16 symptomatic, 6 asymptomatic, total duration of ischemia 228 minutes) occurred in the patients treated with heparin alone. Kaplan-Meier analysis demonstrated a significantly higher probability of being ischemia free in the group of patients treated with rt-PA followed by heparin compared with the group treated with heparin alone ($p < 0.01$) (Figure 1).

Coronary arteriographic findings: At baseline there was no significant differences between those treated with heparin alone and those treated with rt-PA plus heparin with regard to quantitative and qualitative angiographic findings (Table II). After the 72-hour follow-up period, only 20 patients repeated coronary arteriography. Two patients (1 in the heparin-alone group and 1 in the rt-PA-plus-heparin group) refused the procedure and in another patient the procedure was not accomplished because of a bleeding complication after rt-PA infusion. In both groups there were no significant differences in the results of quantitative analysis performed before randomization when compared with postinfusion values. However, at repeat study, in 1 patient after rt-PA administration, an occlusive thrombus was found to have recanalized and the filling defects disappeared, whereas 1 patient treated with heparin alone developed total occlusion of the ischemia-producing artery without evidence of myocardial infarction.

In the rt-PA-plus-heparin group, major bleeding and hematoma at the puncture site occurred in 1 patient and 4 patients had minor bleeding during infusion. One patient treated with heparin alone developed a large retroperitoneal hematoma after the second coronary arteriography. Blood transfusion was required only in this patient.

In-hospital follow-up: After the 72-hour follow-up period, 2 of 11 patients in the rt-PA plus-heparin group remained symptom free and were discharged on medical treatment. Both patients were given an antiplatelet regimen. One patient had an uncomplicated myocardial infarction 15 days after discharge. The remaining 9 patients had recurrence of ischemic attacks during hospitalization. Three patients underwent emergency percutaneous transluminal coronary angioplasty and 3 had the procedure electively. Three patients underwent elective coronary artery bypass surgery. In the heparin-

alone group all patients had persistence of unstable angina. Two had uncomplicated myocardial infarction. One patient, who was not suitable for coronary revascularization, died because of cardiogenic shock due to massive myocardial infarction. Two patients underwent emergency percutaneous transluminal coronary angioplasty and 5 required emergency coronary artery bypass grafting. Two patients underwent elective percutaneous transluminal coronary angioplasty. Although the number of patients who had revascularization or myocardial infarction was similar in the 2 groups, the cumulative number of emergency procedures plus myocardial infarctions was higher in the group treated with heparin alone (10 versus 4 patients).

TABLE II Qualitative and Quantitative Analysis of the Ischemia-Related Lesion Before and After Each Treatment

	rt-PA + Heparin (9 patients)		Heparin (11 patients)	
Characteristics	Before	After	Before	After
Concentric	3	3	4	4
Type I eccentric	0	0	2	2
Type II eccentric	3	3	2	1
Multiple irregularities	2	3	2	2
Total occlusion	1	0	1	2
Intracoronary thrombus	2	1	2	3
Diameter stenosis (%)	67 ± 13	58 ± 18	63 ± 23	61 ± 25
Area stenosis (%)	85 ± 12	84 ± 16	81 ± 18	80 ± 15

Qualitative results are expressed as number of patients; quantitative results are expressed as mean ± standard deviation. There were no significant differences before and after treatment for each group.

DISCUSSION

Conventional medical treatment in unstable angina: The pathophysiology of unstable angina is complex, but in most patients it appears to involve an interaction between fixed atherosclerotic coronary stenosis and dynamic coronary obstruction mediated by either coronary vasoconstriction or transient thrombotic occlusion.[20,21] The initial management usually involves a trial of intensive medical therapy with β blockers, calcium channel blockers, nitrates and aspirin. Although chest pain is often controlled in the coronary care unit, a substantial percentage of patients remain symptomatic.[1-4] These patients, refractory to conventional medical treatment, have a greater incidence of early myocardial infarction or death than patients whose symptoms subside.[1,8,9] Our prospective study demonstrates that unstable angina refractory to conventional medical treatment occurs in about one-fourth of the patients admitted to the hospital with the diagnosis of unstable angina.

Clinical, electrocardiographic and angiographic features, including qualitative analysis of the ischemia-related lesion and the presence of intracoronary thrombi, failed to identify any difference between patients in whom stabilization was achieved with conventional medical treatment and those who were refractory.

Anticoagulation and thrombolysis in unstable angina: Two definitive trials have clearly demonstrated that the addition of heparin to conventional therapy improves the early management of unstable angina. Theroux,[14] Neri Serneri[15] and their co-workers, confirming previous observations by Telford and Wilson,[13] showed that the administration of heparin in the acute phase of unstable angina significantly reduces symptoms and signs of myocardial ischemia and the incidence of myocardial infarction and refractory angina. Previous intervention studies have also suggested that the outcome in patients with unstable angina may be improved by thrombolytic therapy. The studies by Lawrence,[16] Gold[17] and their co-workers demonstrated that thrombolysis significantly reduces the incidence of ischemic attacks and myocardial infarction in unstable angina. On the contrary, more recently, Nicklas,[22] Topol[23] and their co-workers showed that intravenous rt-PA does not ensure a clinical benefit and does not eliminate the need for revascularization. Our results demonstrate that thrombolytic treatment with rt-PA followed by heparin is superior than heparin alone for the prevention of recurrent ischemic attacks in the short term in patients with unstable angina refractory to conventional medical treatment. The uniqueness of our study population makes comparisons with previous studies on the effect

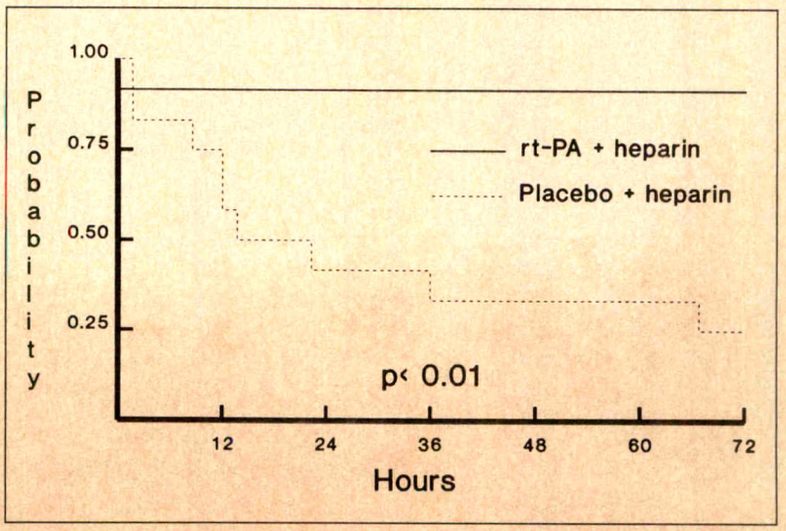


FIGURE 1. Kaplan-Meier curves comparing (according to an intention-to-treat analysis) the probability of being ischemia free during a period of 72 hours in the 24 patients with unstable angina refractory to conventional medical treatment. A statistical significance was found between patients treated with recombinant tissue-type plasminogen activator (rt-PA) plus heparin and those treated with heparin alone ($p < 0.01$).

of thrombolytic therapy in unstable angina difficult and questionable. The only study[15] that focused on refractory patients has demonstrated that thrombolysis decreases the frequency of angina on the day of infusion but not in the following days. These results, in contrast with our data, may be explained by the fact that heparin was not given after thrombolytic therapy as it was in our study. The question of whether thrombolysis may improve angiographic findings in unstable angina is also still debated. Vetrovec,[21] Mandelkorn[24] and more recently De Zwaan[25] and their co-workers found clinical improvement in patients with unstable angina treated with streptokinase or rt-PA, although in most patients only minor angiographic improvements in percentage diameter stenosis were present. Ambrose,[19] Nicklas[22] and their co-workers reported that thrombolysis is of limited utility in either unstable angina or recent non-Q-wave myocardial infarction. In our study, neither rt-PA followed by heparin nor heparin alone induced significant changes in the outcome of quantitative or qualitative analysis of the ischemia-related lesion. Because the group randomized for combined treatment had a significant clinical improvement in the short term without changes in angiography, one could hypothesize that the contribution of intracoronary thrombus to the total coronary stenosis may be relatively minor and therefore difficult to detect. In fact, in a study reported by Sherman et al,[10] intraoperative coronary angioscopy was performed in 10 patients with unstable angina refractory to conventional medical therapy. They found that 3 patients had complex plaques, whereas 7 patients had intracoronary thrombi that were detected correctly by coronary angiography in only 1 of them. Moreover, the significant delay (>72 hours) between thrombolytic therapy and angiographic restudy, allowing reappearance of thrombus, may have complicated the correlation between clinical benefit and poor angiographic results.

Limitations: A possible limitation of this study may be represented by the regimen used for the heparin treatment. The choice of heparin, 5,000 IU 4 times daily, was made on the basis of the available demonstration of the beneficial effect of such dose in unstable angina.[13] Recently, Neri Serneri et al[15] found that heparin infusion is superior to intermittent bolus administration in reducing symptoms and signs of ischemia (mean reduction with heparin infusion 80%, with heparin boluses 25%). In our study, about 80% reduction in the number and total duration of ischemic episodes was also documented in the group of patients treated with heparin bolus alone. The discrepancy between the 2 studies may be explained by the fact that in our protocol the APTT was monitored in order to maintain it within the therapeutic range, while in the Neri Serneri[15] study the APTT was checked once daily and for overdose avoidance only. No dose adjustment was provided in case of underdosing.

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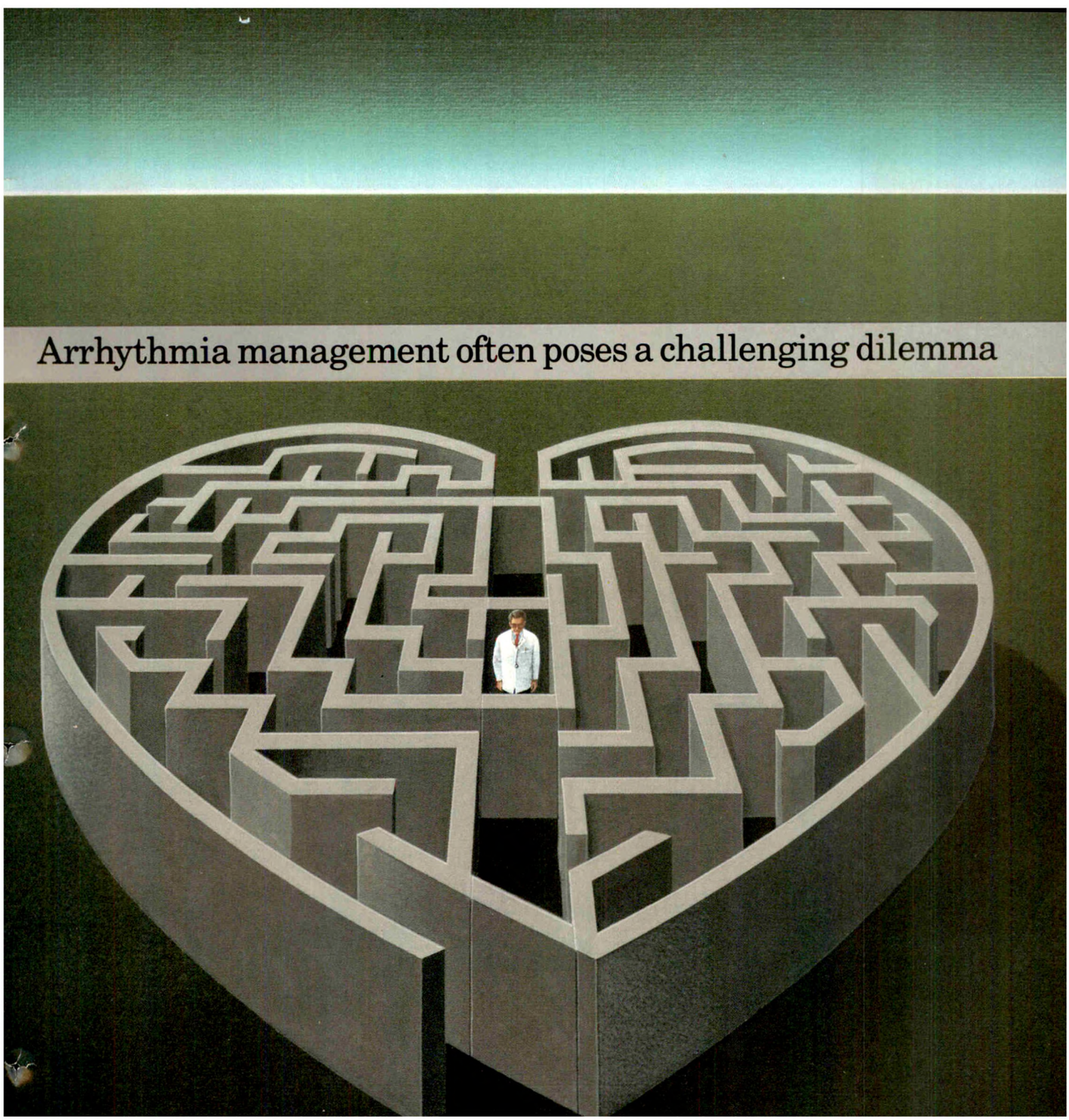
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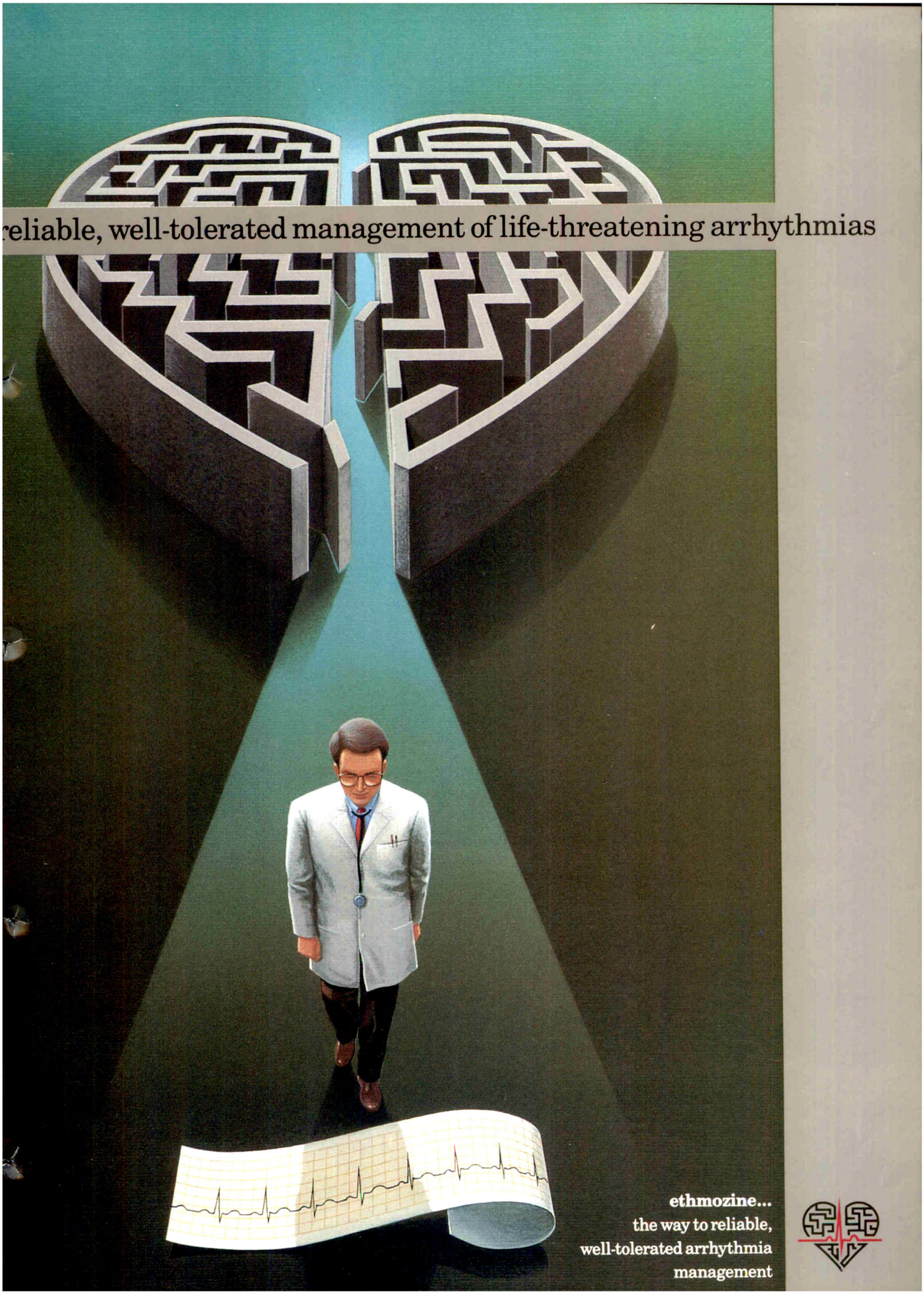
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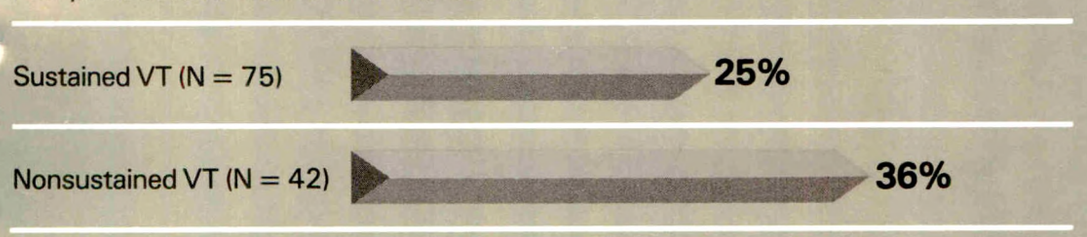
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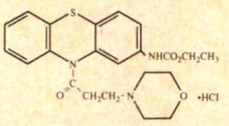
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6217/June, 1990

ETHMOZINE®
(moricizine hydrochloride)
TABLETS

DESCRIPTION
ETHMOZINE (moricizine hydrochloride) is an orally active antiarrhythmic drug available for administration in tablets containing 200 mg, 250 mg and 300 mg of moricizine hydrochloride. The chemical name of moricizine hydrochloride is 10-(3-morpholinopropionyl) phenothiazine-2-carbamic acid ethyl ester hydrochloride and the structural formula is represented as follows:



MW = 464

Moricizine hydrochloride is a white to tan crystalline powder, freely soluble in water and has a pKa of 6.4 (weak base). ETHMOZINE tablets contain: lactose, microcrystalline cellulose, sodium starch glycolate, magnesium stearate and dyes (FD&C Blue 1, D&C Yellow 10 and FD&C Yellow 6 [200 mg tablet]; FD&C Yellow 6 and FD&C Red 40 [250 mg tablet]; FD&C Blue 1 [300 mg tablet]).

CLINICAL PHARMACOLOGY
Mechanism of Action
ETHMOZINE is a Class I antiarrhythmic agent with potent local anesthetic activity and myocardial membrane stabilizing effect. ETHMOZINE reduces the fast inward current carried by sodium ions.

In isolated dog Purkinje fibers, ETHMOZINE shortens Phase II and III repolarization, resulting in a decreased action potential duration and effective refractory period. A dose-related decrease in the maximum rate of Phase 0 depolarization (V_{max}) occurs without effect on maximum diastolic potential or action potential amplitude. The sinus node and atrial tissue of the dog are not affected.

Electrophysiology
Electrophysiology studies in patients with ventricular tachycardia have shown that ETHMOZINE, at daily doses of 750 mg and 900 mg, prolongs atrioventricular conduction. Both AV nodal conduction time (AH interval) and His-Purkinje conduction time (HV interval) are prolonged by 10-13% and 21-26%, respectively. The PR interval is prolonged by 16-20% and the QRS by 7-18%. Prolongations of 2-5% in the corrected QT interval result from widening of the QRS interval, but there is shortening of the JT interval, indicating an absence of significant effect on ventricular repolarization. Intra-atrial conduction or atrial effective refractory periods are not consistently affected. In patients without sinus node dysfunction, ETHMOZINE has minimal effects on sinus cycle length and sinus node recovery time. These effects may be significant in patients with sinus node dysfunction (see PRECAUTIONS: Electrocardiographic Changes/Conduction Abnormalities).

Hemodynamics
In patients with impaired left ventricular function, ETHMOZINE has minimal effects on measurements of cardiac performance such as cardiac index, stroke volume index, pulmonary capillary wedge pressure, systemic or pulmonary vascular resistance or ejection fraction, either at rest or during exercise. ETHMOZINE is associated with a small, but consistent increase in resting blood pressure and heart rate. Exercise tolerance in patients with ventricular arrhythmias is unaffected. In patients with a history of congestive heart failure or angina pectoris, exercise duration and rate-pressure product at maximal exercise are unchanged during ETHMOZINE administration. Nonetheless, in some cases worsened heart failure in patients with severe underlying heart disease has been attributed to ETHMOZINE.

Other Pharmacologic Effects
Although ETHMOZINE is chemically related to the neuroleptic phenothiazines, it has no demonstrated central or peripheral dopaminergic activity in animals. Moreover, in patients on chronic ETHMOZINE, serum prolactin levels did not increase.

Pharmacokinetics/Pharmacodynamics
The antiarrhythmic and electrophysiologic effects of ETHMOZINE are not related in time, course, or intensity to plasma moricizine concentrations or to the concentrations of any identified metabolite, all of which have short (2-3 hours) half-lives. Following single doses of ETHMOZINE, there is a prompt prolongation of the PR interval, which becomes normal within 2 hours, consistent with the rapid fall of plasma moricizine. JT interval shortening, however, peaks at about 6 hours and persists for at least 10 hours. Although an effect on VPD rates is seen within 2 hours after dosing, the full effect is seen after 10-14 hours and persists in full, when therapy is terminated, for more than 10 hours, after which the effect decays slowly, and is still substantial at 24 hours. This suggests either an unidentified, active, long half-life metabolite or a structural or functional "deep compartment" with slow entry from, and release to, the plasma. The following description of parent compound pharmacokinetics is therefore of uncertain relevance to clinical actions.

Following oral administration, ETHMOZINE undergoes significant first-past metabolism resulting in an absolute bioavailability of approximately 38%. Peak plasma concentrations of ETHMOZINE are usually reached within 0.5-2 hours. Administration 30 minutes after a meal delays the rate of absorption, resulting in lower peak plasma concentrations, but the extent of absorption is not altered. ETHMOZINE plasma levels are proportional to dose over the recommended therapeutic dose range.

The apparent volume of distribution after oral administration is very large (≥300 L) and is not significantly related to body weight. ETHMOZINE is approximately 95% bound to human plasma proteins. This binding interaction is independent of ETHMOZINE plasma concentration.

ETHMOZINE undergoes extensive biotransformation. Less than 1% of orally administered ETHMOZINE is excreted unchanged in the urine. There are at least 26 metabolites, but no single metabolite has been found to represent as much as 1% of the administered dose, and as stated above, antiarrhythmic response has relatively slow onset and offset. Two metabolites are pharmacologically active in at least one animal model: moricizine sulfoxide and phenothiazine-2-carbamic acid ethyl ester sulfoxide. Each of these metabolites represents a small percentage of the administered dose (< 0.6%), is present in lower concentrations in the plasma than the parent drug, and has a plasma elimination half-life of approximately three hours.

ETHMOZINE has been shown to induce its own metabolism. Average ETHMOZINE plasma concentrations in patients decrease with multiple dosing. This decrease in plasma levels of parent drug does not appear to affect clinical outcome for patients receiving chronic ETHMOZINE therapy.

The plasma half-life of ETHMOZINE is 1.5-3.5 hours (most values about 2 hours) following single or multiple oral doses in patients with ventricular ectopy. Approximately 56% of the administered dose is excreted in the feces and 39% is excreted in the urine. Some ETHMOZINE is also recycled through enterohepatic circulation.

CLINICAL ACTIONS
ETHMOZINE at daily doses of 600-900 mg produces a dose-related reduction in the occurrence of frequent premature ventricular depolarizations (VPDs) and reduces the incidence of nonsustained and sustained ventricular tachycardia (VT). In controlled clinical trials, ETHMOZINE has been shown to have antiarrhythmic activity that is generally similar to that of disopyramide, propranolol and quinidine at the doses studied. In programmed electrical stimulation studies (PES), ETHMOZINE prevented the induction of sustained ventricular tachycardia in approximately 25% of patients. Activity of ETHMOZINE is maintained during long-term use.

ETHMOZINE is effective in treating ventricular arrhythmias in patients with and without organic heart disease. ETHMOZINE may be effective in patients in whom other antiarrhythmic agents are ineffective, not tolerated and/or contraindicated.

Arrhythmia exacerbation or "rebound" is not noted following discontinuation of ETHMOZINE therapy.

INDICATIONS AND USAGE
ETHMOZINE is indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that, in the judgement of the physician are life-threatening. Because of the proarrhythmic effects of ETHMOZINE, its use should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks.

Initiation of ETHMOZINE treatment, as with other antiarrhythmic agents used to treat life-threatening arrhythmias, should be carried out in the hospital.

Antiarrhythmic drugs have not been proven to improve survival in patients with ventricular arrhythmias.

CONTRAINDICATIONS
ETHMOZINE is contraindicated in patients with preexisting second- or third-degree AV block and in patients with right bundle branch block when associated with left hemiblock (bifascicular block) unless a pacemaker is present. ETHMOZINE is also contraindicated in the presence of cardiogenic shock or known hypersensitivity to the drug.

WARNINGS
Mortality
ETHMOZINE was one of three antiarrhythmic drugs included in the National Heart Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term multicenter, randomized, double-blind study in patients with asymptomatic nonlife-threatening arrhythmias who had a myocardial infarction more than 6 days, but less than 2 years, previously. An excessive mortality or nonfatal cardiac arrest rate was seen in patients treated with both of the Class IC agents included in the trial, which led to discontinuation of those 2 arms of the trial. The ETHMOZINE and placebo arms of the trial are continuing.

The applicability of the CAST results to other populations (e.g. those without recent myocardial infarction) and to agents other than IC (particularly to ETHMOZINE which, at this time remains in the trial) is uncertain. Considering the known proarrhythmic properties of ETHMOZINE and the lack of evidence of improved survival for any antiarrhythmic drug in patients without life-threatening arrhythmias, it is prudent to reserve the use of ETHMOZINE, as well as other antiarrhythmic agents, for patients with life-threatening ventricular arrhythmias.

Proarrhythmia
Like other antiarrhythmic drugs, ETHMOZINE can provoke new rhythm disturbances or make existing arrhythmias worse. These proarrhythmic effects can range from an increase in the frequency of VPDs to the development of new or more severe ventricular tachycardia, e.g. tachycardia that is more sustained or more resistant to conversion to sinus rhythm, with potentially fatal consequences. It is often not possible to distinguish a proarrhythmic effect from the patient's underlying rhythm disorder, so that the occurrence rates given below must be considered approximations. Note also that drug-induced arrhythmias can generally be identified only when they occur early after starting the drug and when the rhythm can be identified, usually because the patient is being monitored. It is clear from the NIH-sponsored CAST (Cardiac Arrhythmia Suppression Trial) that some antiarrhythmic drugs can cause increased sudden death mortality, presumably due to new arrhythmias or asystole that do not appear early after treatment but that represent a sustained increased risk.

Domestic premarketing trials included 1072 patients given ETHMOZINE; 397 had baseline lethal arrhythmias (sustained VT or VF and nonsustained VT with hemodynamic symptoms) and 576 had potentially lethal arrhythmias (increased VPDs or NSVT in patients with known structural heart disease, active ischemia, congestive heart failure or an LVEF < 40% and/or CI < 2.0 1/min/m2). In this population there were 40 (3.7%) identified proarrhythmic events, 26 (2.5%) of which were serious, either fatal (6), new hemodynamically significant sustained VT or VF (4), new sustained VT that was not hemodynamically significant (11) or sustained VT that became syncopal/presyncopal when it had not been before (5).

In general, serious proarrhythmic effects were equally common in patients with more and less severe arrhythmias, 2.5% in the patients with baseline lethal arrhythmias vs. 2.8% in patients with potentially lethal arrhythmias, although the patients with serious effects were more likely to have a history of sustained VT (38% vs. 23%).

Five of the six fatal proarrhythmic events were in patients with baseline lethal arrhythmias; four had prior cardiac arrests. Rates and severity of proarrhythmic events were similar in patients given 600-900 mg of ETHMOZINE per day and those given higher doses. Patients with proarrhythmic events were more likely than the overall population to have coronary artery disease (85% vs. 67%), history of acute myocardial infarction (75% vs. 53%), congestive heart failure (60% vs. 43%), and cardiomegaly (55% vs. 33%). All of the six proarrhythmic deaths were in patients with coronary artery disease; 5/6 each had documented acute myocardial infarction, congestive heart failure, and cardiomegaly.

Electrolyte Disturbances
Hypokalemia, hyperkalemia or hypomagnesemia may alter the effects of Class I antiarrhythmic drugs. Electrolyte imbalances should be corrected before administration of ETHMOZINE.

Sick Sinus Syndrome
ETHMOZINE should be used only with extreme caution in patients with sick sinus syndrome, as it may cause sinus bradycardia, sinus pause or sinus arrest.

PRECAUTIONS
General:
Electrocardiographic Changes/Conduction Abnormalities
ETHMOZINE slows AV nodal and intraventricular conduction, producing dose-related increases in the PR and QRS intervals. In clinical trials, the average increase in the PR interval was 12% and the QRS interval was 14%. Although the QTC interval is increased, this is wholly because of QRS prolongation; the JT interval is shortened, indicating the absence of significant slowing of ventricular repolarization. The degree of lengthening of PR and QRS intervals does not predict efficacy.

In controlled clinical trials and in open studies, the overall incidence of delayed ventricular conduction, including new bundle branch block pattern, was approximately 9.4%. In patients without baseline conduction abnormalities, the frequency of second-degree AV block was 0.2% and third-degree AV block did not occur. In patients with baseline conduction abnormalities, the frequencies of second-degree AV block and third-degree AV block were 0.9% and 1.4%, respectively.

ETHMOZINE therapy was discontinued in 1.6% of patients due to electrocardiographic changes (0.6% due to sinus pause or asystole, 0.2% to AV block, 0.2% to junctional rhythm, 0.4% to intraventricular conduction delay, and 0.2% to wide QRS and/or PR interval).

In patients with preexisting conduction abnormalities, ETHMOZINE therapy should be initiated cautiously. If second- or third-degree AV block occurs, ETHMOZINE therapy should be discontinued unless a ventricular pacemaker is in place. When changing the dose of ETHMOZINE or adding concomitant medications which may also affect cardiac conduction, patients should be monitored electrocardiographically.

Hepatic Impairment
Patients with significant liver dysfunction have reduced plasma clearance and an increased half-life of ETHMOZINE. Although the precise relationship of ETHMOZINE levels to effect is not clear, patients with hepatic disease should be treated with lower doses and closely monitored for excessive pharmacological effects, including effects on ECG intervals, before dosage adjustment. Patients with severe liver disease should be administered ETHMOZINE with particular care, if at all. (See DOSAGE AND ADMINISTRATION)

Renal Impairment
Plasma levels of intact ETHMOZINE are unchanged in hemodialysis patients, but a significant portion (39%) of ETHMOZINE is metabolized and excreted in the urine. Although no identified active metabolite is known to increase in people with renal failure, metabolites of unrecognized importance could be affected. For this reason, ETHMOZINE should be administered cautiously in patients with impaired renal function. Patients with significant renal dysfunction should be started on lower doses and monitored for excessive pharmacologic effects, including ECG intervals, before dosage adjustment. (See DOSAGE AND ADMINISTRATION)

Congestive Heart Failure
Most patients with congestive heart failure have tolerated the recommended ETHMOZINE daily doses without unusual toxicity or change in effect. Pharmacokinetic differences between ETHMOZINE patients with and without congestive heart failure were not apparent (see Hepatic Impairment above). In some cases, worsened heart failure has been attributed to ETHMOZINE. Patients with preexisting heart failure should be monitored carefully when ETHMOZINE is initiated.

Effects on Pacemaker Threshold
The effect of ETHMOZINE on the sensing and pacing thresholds of artificial pacemakers has not been sufficiently studied. In such patients, pacing parameters must be monitored, if ETHMOZINE is used.

Drug Interactions
No significant changes in serum digoxin levels or pharmacokinetics have been observed in patients or healthy subjects receiving concomitant ETHMOZINE therapy. Concomitant use was associated with additive prolongation of the PR interval, but not with a significant increase in the rate of second- or third-degree AV block.

Concomitant administration of cimetidine resulted in a decrease in ETHMOZINE clearance of 49% and a 1.4 fold increase in plasma levels in healthy subjects. During clinical trials, no significant changes in the efficacy or tolerance of ETHMOZINE have been observed in patients receiving concomitant cimetidine therapy. Patients on cimetidine should have ETHMOZINE therapy initiated at relatively low doses, not more than 600 mg/day. Patients should be monitored when concomitant cimetidine therapy is instituted or discontinued or when the ETHMOZINE dose is changed.

Concomitant administration of beta blocker therapy did not reveal significant changes in overall electrocardiographic intervals in patients. In one controlled study, ETHMOZINE and propranolol administered concomitantly produced a small additive increase in the PR interval.

Theophylline clearance and plasma half-life were significantly affected by multiple dose ETHMOZINE administration when both conventional and sustained release theophylline were given to healthy subjects (clearance increased 44-66% and plasma half-life decreased 19-33%). Plasma theophylline levels should be monitored when concomitant ETHMOZINE is initiated or discontinued.

Because of possible additive pharmacologic effects, caution is indicated when ETHMOZINE is used with any drug that affects cardiac electrophysiology. Uncontrolled experience in patients indicates no serious adverse interaction during the concomitant use of ETHMOZINE and diuretics, vasodilators, antihypertensive drugs, calcium channel blockers, beta blockers, ACE inhibitors, and warfarin. Plasma warfarin levels, warfarin pharmacokinetics, and prothrombin times were unaffected during multiple dose ETHMOZINE administration to healthy subjects.

Results from *in vitro* studies do not suggest alterations in ETHMOZINE plasma protein binding in the presence of other highly plasma protein bound drugs.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

In a 24-month mouse study in which ETHMOZINE was administered in the feed at concentrations calculated to provide doses ranging up to 320 mg/kg/day, ovarian tubular adenomas and granulosa cell tumors were limited in occurrence to ETHMOZINE treated animals. Although the findings were of borderline statistical significance, or not statistically significant, historical control data indicate that both of these tumors are uncommon in the strain of mouse studied.

In a 24-month study in which ETHMOZINE was administered by gavage to rats at doses of 25, 50 and 100 mg/kg/day, Zymbal's Gland Carcinoma was observed in one mid-dose and two high-dose males. This tumor appears to be uncommon in the strain of rat studied. Rats of both sexes also showed a dose-related increase in hepatocellular cholangioma (also described as bile ductile cystadenoma or cystic hyperplasia) along with fatty metamorphosis, possibly due to disruption of hepatic choline utilization for phospholipid biosynthesis. The rat is known to be uniquely sensitive to alteration in choline metabolism.

ETHMOZINE was not mutagenic when assayed for genotoxicity in *in vitro* bacterial (Ames test) and mammalian (Chinese hamster ovary/hypoxanthine-guanine phosphoribosyl transferase and sister chromatid exchange) cell systems or in *in vivo* mammalian systems (rat bone cytogenicity and mouse micronucleus).

A general reproduction and fertility study was conducted in rats at dose levels up to 6.7 times the maximum recommended human dose of 900 mg/day (based upon 50 kg human body weight) and revealed no evidence of impaired male or female fertility.

Pregnancy—Teratogenic Effects:
Pregnancy Category B

Teratology studies have been performed with ETHMOZINE in rats and in rabbits at doses up to 6.7 and 4.7 times the maximum recommended human daily dose, respectively, and have revealed no evidence of harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ETHMOZINE should be used during pregnancy only if clearly needed.

Pregnancy—Nonteratogenic Effects:

In a study in which rats were dosed with ETHMOZINE prior to mating, during mating and throughout gestation and lactation, dose levels 3.4 and 6.7 times the maximum recommended human daily dose produced a dose-related decrease in pup and maternal weight gain, possibly related to a larger litter size. In a study in which dosing was begun on Day 15 of gestation, ETHMOZINE, at a level 6.7 times the maximum recommended human daily dose, produced a retardation in maternal weight gain but no effect on pup growth.

Nursing Mothers

ETHMOZINE is secreted in the milk of laboratory animals and has been reported to be present in human milk. Because of the potential for serious adverse reactions in nursing infants from ETHMOZINE, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of ETHMOZINE in children less than 18 years of age have not been established.

ADVERSE REACTIONS

The most serious adverse reaction reported for ETHMOZINE is proarrhythmia (see WARNINGS). This occurred in 3.7% of 1072 patients with ventricular arrhythmias who received a wide range of doses under a variety of circumstances.

In addition to discontinuations because of proarrhythmias, in controlled clinical trials and in open studies, adverse reactions led to discontinuation of ETHMOZINE in 7% of 1105 patients with ventricular and supraventricular arrhythmias, including 3.2% due to nausea, 1.6% due to ECG abnormalities (principally conduction defects, sinus pause, junctional rhythm, or AV block), 1% due to congestive heart failure, and 0.3-0.4% due to dizziness, anxiety, drug fever, urinary retention, blurred vision, gastrointestinal upset, rash, and laboratory abnormalities.

The most frequently occurring adverse reactions in the 1072 patients (including all adverse experiences whether or not considered ETHMOZINE-related by the investigator) were dizziness (15.1%), nausea (9.6%), headache (8.0%), fatigue (5.9%), palpitations (5.8%), and dyspnea (5.7%). Dizziness appears to be related to the size of each dose. In a comparison of 900 mg/day given at 450 mg b.i.d. or 300 mg t.i.d., more than 20% of patients experienced dizziness on the b.i.d. regimen vs. 12% on the t.i.d. regimen.

Adverse reactions reported by less than 5%, but in 2% or greater of the patients were: sustained ventricular tachycardia, hypesthesia, abdominal pain, dyspepsia, vomiting, sweating, cardiac chest pain, asthenia, nervousness, paresthesia, congestive heart failure, musculoskeletal pain, diarrhea, dry mouth, cardiac death, sleep disorders, and blurred vision.

Adverse reactions infrequently reported (in less than 2% of patients) were:

Cardiovascular hypotension, hypertension, syncope, supraventricular arrhythmias (including atrial fibrillation/flutter), cardiac arrest, bradycardia, pulmonary embolism, myocardial infarction, vasodilation, cerebrovascular events, thrombophlebitis;
Nervous System tremor, anxiety, depression, euphoria, confusion, somnolence, agitation, seizure, coma, abnormal gait, hallucinations, nystagmus, diplopia, speech disorder, akathisia, loss of memory, ataxia, abnormal coordination, dyskinesia, vertigo, tinnitus;
Genitourinary urinary retention or frequency, dysuria, urinary incontinence, kidney pain, impotence, decreased libido;
Respiratory hyperventilation, apnea, asthma, pharyngitis, cough, sinusitis;
Gastrointestinal anorexia, bitter taste, dysphagia, flatulence, ileus;
Other drug fever, hypothermia, temperature intolerance, eye pain, rash, pruritus, dry skin, urticaria, swelling of the lips and tongue, periorbital edema.

During ETHMOZINE therapy, two patients developed thrombocytopenia that may have been drug-related. Clinically significant elevations in liver function tests (bilirubin, serum transaminases) and jaundice consistent with hepatitis were rarely reported. Although a cause and effect relationship has not been established, caution is advised in patients who develop unexplained signs of hepatic dysfunction, and consideration should be given to discontinuing therapy.

Three patients developed rechallenge-confirmed drug fever, with one patient experiencing an elevation above 103°F (to 105°F, with rigors). Fevers occurred at about 2 weeks in 2 cases, and after 21 weeks in the third. Fevers resolved within 48 hours of discontinuation of moricizine.

Adverse reactions were generally similar in patients over 65 (n=375) and under 65 (n=697), although discontinuation of therapy for reasons other than proarrhythmia was more common in older patients (13.9% vs. 7.7%). Overall mortality was greater in older patients (9.3% vs. 3.9%), but those were not deaths attributed to treatment and the older patients had more serious underlying heart disease.

The following table compares the most common (occurrence in more than 2% of the patients) noncardiac adverse reactions (i.e., drug-related or of unknown relationship) in controlled clinical trials during the first one to two weeks of therapy with ETHMOZINE, quinidine, placebo, disopyramide, or propranolol in patients with ventricular arrhythmias.

INCIDENCE (%) OF THE MOST COMMON ADVERSE REACTIONS (THERAPY DURATION = 1-14 DAYS)

Adverse Reactions	>2% Moricizine		>2% Placebo		>2% Quinidine		>5% Disopyramide		>5% Propranolol	
	No.	%	No.	%	No.	%	No.	%	No.	%
Total No. of Patients	1072		618		110		31		24	
Dizziness	121	11.3	33	5.3	8	7.3	–		2	8.3
Nausea	74	6.9	18	2.9	7	6.4	3	9.7	–	
Headache	62	5.8	27	4.4	–		–		4	16.7
Pain	41	3.8	31	5.0	6	5.5	2	6.5	–	
Dyspnea	41	3.8	22	3.6	–		–		–	
Hypesthesia	40	3.7	–		3	2.7	–		–	
Fatigue	33	3.1	16	2.6	6	5.5	2	6.5	3	12.5
Vomiting	22	2.1	–		–		–		–	
Dry Mouth	–		–		–		11	35.5	–	
Nervousness	–		–		–		3	9.7	–	
Blurred Vision	–		–		3	2.7	2	6.5	3	12.5
Diarrhea	–		–		25	22.7	–		–	
Constipation	–		–		–		2	6.5	–	
Somnolence	–		–		–		–		2	8.3
Urinary Retention	–		–		–		4	12.9	–	

OVERDOSAGE

Deaths have occurred after accidental or intentional overdosages of 2,250 and 10,000 mg of ETHMOZINE, respectively.

Signs, Symptoms and Laboratory Findings Associated with an Overdosage of Drug

Overdosage with ETHMOZINE may produce emesis, lethargy, coma, syncope, hypotension, conduction disturbances, exacerbation of congestive heart failure, myocardial infarction, sinus arrest, arrhythmias, (including junctional bradycardia, ventricular tachycardia, ventricular fibrillation and asystole), and respiratory failure.

Lethal Dose in Animals

Oral doses of ETHMOZINE of about 200 mg/kg in dogs, 250 mg/kg in monkeys, 420 mg/kg in mice and 905 mg/kg in rats were lethal to about one-half of the animals exposed. Death was usually preceded by tremors, convulsions and respiratory depression.

Recommended General Treatment Procedures

A specific antidote for ETHMOZINE has not been identified. In the event of overdosage, treatment should be supportive. Patients should be hospitalized and monitored for cardiac, respiratory and CNS changes. Advanced life support systems, including an intracardiac pacing catheter, should be provided where necessary. Acute overdosage should be treated with appropriate gastric evacuation, and with special care to avoid aspiration. Accidental introduction of ETHMOZINE into the lungs of monkeys resulted in rapid arrhythmic death.

DOSAGE AND ADMINISTRATION

The dosage of ETHMOZINE must be individualized on the basis of antiarrhythmic response and tolerance. Clinical, cardiac rhythm monitoring, electrocardiogram intervals, exercise testing, and/or programmed electrical stimulation testing may be used to guide antiarrhythmic response and dosage adjustment. In general, the patients will be at high risk and should be hospitalized for the initiation of therapy (see INDICATIONS AND USAGE).

The usual adult dosage is between 600 and 900 mg per day, given every 8 hours in three equally divided doses. Within this range, the dosage can be adjusted as tolerated, in increments of 150 mg/day at 3-day intervals, until the desired effect is obtained. Patients with life-threatening arrhythmias who exhibit a beneficial response as judged by objective criteria (Holter monitoring, programmed electrical stimulation, exercise testing, etc.) can be maintained on chronic ETHMOZINE therapy. As the antiarrhythmic effect of ETHMOZINE persists for more than 12 hours, some patients whose arrhythmias are well controlled on a Q8H regimen may be given the same total daily dose in a Q12H regimen to increase convenience and help assure compliance. When higher doses are used, patients may experience more dizziness and nausea on the Q12H regimen.

Patients with Hepatic Impairment

Patients with hepatic disease should be started at 600 mg/day or lower and monitored closely, including measurement of ECG intervals, before dosage adjustment.

Patients with Renal Impairment

Patients with significant renal dysfunction should be started at 600 mg/day or lower and monitored closely, including measurement of ECG intervals, before dosage adjustment.

Transfer to ETHMOZINE

Recommendations for transferring patients from another antiarrhythmic to ETHMOZINE can be given based on theoretical considerations. Previous antiarrhythmic therapy should be withdrawn for 1-2 plasma half-lives before starting ETHMOZINE at the recommended dosages. In patients in whom withdrawal of a previous antiarrhythmic is likely to produce life-threatening arrhythmias, hospitalization is recommended.

Transferred From	Start ETHMOZINE
Quinidine, Disopyramide	6-12 hours after last dose
Procainamide	3-6 hours after last dose
Encainide, Propafenone, Tocainide, or Mexiletine	8-12 hours after last dose
Flecainide	12-24 hours after last dose

HOW SUPPLIED

ETHMOZINE (moricizine hydrochloride) is available as oval, convex, film-coated tablets as follows:

200 mg (light green):	Bottles of 100 (NDC 0056-0061-70) Hospital Unit Dose Carton of 100 (NDC 0056-0061-75)
250 mg (light orange):	Bottles of 100 (NDC 0056-0062-70) Hospital Unit Dose Carton of 100 (NDC 0056-0062-75)
300 mg (light blue):	Bottles of 100 (NDC 0056-0064-70) Hospital Unit Dose Carton of 100 (NDC 0056-0064-75)

Store at controlled room temperature (59°-86°F, 15°-30°C) in a tightly-closed, light-resistant container. Keep in carton until dispensed. Protect from light.

Du Pont Pharmaceuticals
E.I. du Pont de Nemours & Co.
Wilmington, Delaware 19898

DUPONT

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Role Of Beta-Adrenergic Blockers After Percutaneous Transluminal Coronary Angioplasty

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Restenosis after percutaneous transluminal coronary angioplasty (PTCA) cannot currently be prevented. Different medical regimens have been largely unsuccessful. Experimental studies suggest roles for β-adrenergic blockers and calcium antagonists. Controlled clinical studies have failed to show any decrease in restenosis rate for calcium antagonists. Corresponding studies for β blockers are lacking. This study evaluates 541 consecutive PTCA procedures, 455 (86%) in patients treated with β blockers after PTCA (76% metoprotol, 14% atenolol, 4% sotalol, 6% others) and 86 (14%) in patients without β blockers. Angiographic success was achieved in 483 of 620 lesions (78%), and was not significantly different with or without β blockers (79 vs 73%, p >0.05). The procedure success rate and the complication rates (myocardial infarction, emergency coronary artery bypass grafting, death) did not differ with or without β blockers (p >0.05). Follow-up angiograms for 426 of the 483 successfully dilated lesions (88%) revealed that a total of 155 stenoses had recurred (36%). The restenosis rate was not significantly different with (368) or without (58) β blockers (36 vs 38%, p >0.05). For β blockers with calcium antagonists (84% nifedipine, 13% diltiazem, 2% verapamil, 1% others), the restenosis rate was 97 of 250 (39%) vs 36 of 118 (31%) (p >0.05). This retrospective study indicates that treatment with β-adrenergic blockers after PTCA, alone or in combination with calcium antagonists, does not influence either the success rate or the restenosis rate and can be continued if indicated from an antiischemic viewpoint.

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Restenosis after percutaneous transluminal coronary angioplasty (PTCA) remains an unsolved problem. In the decade since the introduction of PTCA,[1] continuing improvements have occurred in success and complication rates,[2] but a restenosis rate of 30 to 45% remains a major concern.[3] The pathophysiology of restenosis after PTCA is still unclear. Various predisposing factors related to lesion, procedure and patient have been identified,[3–5] and different pharmacologic regimens have been tried.[6–10] To date, the medication regimens have been largely unsuccessful. Technical improvements of the angioplasty technique using stents, laser and atherectomy offer hope in reducing the restenosis rates but the efficacy remains to be determined. Regardless of procedure-related improvements, the search to define an optimal medical follow-up treatment continues. There is today strong evidence that intimal hyperplasia is the fundamental process of restenosis.[5] Different drugs may be active during various phases of the response to injury in arterial tissue. Thus, calcium antagonists appear to inhibit the initial phase of smooth muscle proliferation.[11] Clinical studies, however, have failed to show any decrease in the restenosis rates for diltiazem[8] and nifedipine.[9] It has been suggested that β blockers inhibit later phases in the development of intimal hyperplasia.[12] Corresponding clinical studies, however, are lacking. Concern has been expressed regarding the risk for negative effects on the immediate PTCA results by the unopposed α-adrenergic effect during β-blocking treatment.[13] Beta blockers have been shown to reduce the risk for myocardial infarction or sudden death.[14–16] The use of these antiischemic drugs also after successful PTCA has to be considered, since the etiology of the coronary artery disease usually is a remaining concern. The ideal drug would, in addition to its antiischemic properties, decrease the restenosis rate in the absence of any negative effect on the PTCA results. We evaluated the influence of treatment with β blockers on the immediate PTCA results and on the restenosis rates after PTCA. Before considering and planning a prospective, randomized, placebo-controlled trial, a retrospective analysis of the first 541 consecutive PTCA procedures was done.

METHODS

Study population: All PTCA procedures performed between March 1983 and January 1989 were analyzed. During this period 402 patients underwent a total of

TABLE I Clinical Characteristics of Patients Having PTCA Performed With and Without Beta Blockers

	With β blockers	Without β blockers
	No. (%)	No. (%)
Patients (402)*	343	69
Procedures (541)	455 (86)	86 (14)
Age (yrs)		
Mean ± SD	57 ± 10	59 ± 8
Range	25–78	37–73
Men	338 (74)	62 (72)
Smokers		
Previous	178 (39)	30 (35)
Active	92 (20)	16 (19)
Diabetes mellitus	43 (9)	3 (3)
Systemic hypertension	144 (32)	21 (24)
Canadian Heart class		
I	13 (3)	3 (4)
II	65 (14)	7 (8)
III	240 (53)	50 (58)
IV	137 (30)	26 (30)
Indication		
Stable angina	327 (72)	56 (65)
Unstable angina	103 (23)	24 (28)
MI	19 (4)	2 (2)
Silent ischemia	6 (1)	4 (5)
Previous MI	189 (42)	35 (41)
Previous CABG	10 (2)	5 (6)
Previous PTCA	115 (25)	26 (30)

* 343 + 69 = 412 > 402, as 10 patients had multiple PTCAs done both with and without β blockers.
Numbers and percentages refer to the number of procedures with and without β blockers (455 and 86, respectively), except on the second line, where percentages refer to the total number of procedures (541).
CABG = coronary artery bypass grafting; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; SD = standard deviation.

TABLE II Angiographic Characteristics in PTCA Procedures Performed With and Without Beta Blockers

	With β blockers	Without β blockers
	No. (%)	No. (%)
No. of coronary arteries narrowed >50% in diameter*		
1	323 (71)	64 (75)
2	97 (21)	14 (16)
3	35 (8)	8 (9)
Total (541)	455 (100)	86 (100)
Vessel dilated†		
LAD	317 (61)	71 (74)
LC	101 (19)	13 (14)
Right	102 (19)	12 (12)
Graft	4 (1)	0 (0)
Total (620)	524 (100)	96 (100)
Occlusions† (73)	65 (12)	8 (8)
Stenoses† (547)	459 (88)	88 (92)
Mean no. of lesions dilated/procedure	1.15	1.12

* Numbers and percentages refer to the number of procedures with and without β blockers (455 and 86, respectively).
† Numbers and percentages refer to the number of lesions, dilated with and without β-blocker treatment (524 and 96, respectively).
LAD = left anterior descending artery; LC = left circumflex artery; PTCA = percutaneous transluminal coronary angioplasty.

541 procedures, where 620 coronary segments were dilated. The age of the patients was 57 ± 10 years (range 25 to 75), and 74% were men. There was a history of previous myocardial infarction in 41% of the patients; 58% were previous or active smokers, 9% had diabetes and 30% had hypertension. In 26% of the procedures, previous PTCA had been done and in 3% previous coronary artery bypass grafting. The majority of the patients, 84%, had angina pectoris in Canadian Heart class III or IV before PTCA. Treatment with β-adrenergic blockers was maintained during and after 455 procedures (86%), whereas no β blockers were used in 86 procedures (14%). Table I lists the baseline clinical characteristics of the patients with and without β blockers. In the group without β blockers 40 of 69 patients (58%) had previously tried and discontinued treatment with β blockers, whereas 29 patients (42%) had not tried β blockers. Reasons for discontinuing β-blocking treatment were adverse effects for 30 patients (43%) (tiredness 14 patients, bradycardia 7 patients, nightmares 2 patients, headache, mental depression, exanthema, Raynaud's phenomenon, hypotension, atrioventricular block and bronchospasm 1 patient each) and unsatisfactory antianginal effect for 10 patients (15%). The main reason for not trying treatment with β blockers was satisfactory antianginal effect with other medication. This applied to 16 patients (23%). In 13 patients (19%) β blockers were considered contraindicated (asthma 7 patients, intermittent claudication 2 patients, congestive heart failure 2 patients, atrioventricular block and cutaneous porphyria 1 patient each). The 2 groups with and without β blockers in Table I differed only in the proportion of procedures performed in diabetics, which was higher in the β-blocker group, 43 (9%) vs 3 (3%) in the group without β blockers ($p < 0.05$). These 43 PTCA procedures were performed in 32 diabetic patients, 22 of whom (69%) were known diabetics before receiving β blockers, whereas 10 (31%) developed diabetes during β-blocking treatment. The extent of coronary artery disease, defined as the number of vessels with a >50% diameter narrowing, was 1-vessel disease in 71%, 2-vessel disease in 21% and 3-vessel disease in 8%. Of 620 lesions attempted, 547 (89%) were stenoses and 73 (12%) total occlusions. The left anterior descending artery was dilated in 63%, the circumflex and the right coronary artery both in 18% and venous bypass grafts in 1% of the cases. A mean number of 1.15 lesions were dilated per procedure. The angiographic characteristics of the patients with and without β blockers are listed in Table II. The proportion of left anterior descending artery dilation was higher in the group without β blockers, 74 vs 61% ($p < 0.05$); otherwise, the groups did not differ significantly in any of the variables in Table II.

Indications for percutaneous transluminal coronary angioplasty: The PTCA program in our center started in March 1983. In the present study the early results during the training period are included. From 1983 to 1986 a total of 174 procedures were performed with an angiographic success rate of 71%. During the last 2 years of the period studied, 1987 and 1988, a total of 367 procedures were performed, and the angiographic success rates improved to 81%. The proportion of procedures performed in patients treated with β blockers was 83% in 1983 to 1986 and 88% in 1987 to 1988 (p

>0.05). Thus, the evolving changes in indications and the improved immediate PTCA results were not accompanied by any change in the relative proportion of patients treated with β blockers. The indications for PTCA during the whole period, 1983 to 1988, were stable angina pectoris in 71%, unstable angina pectoris in 23%, acute myocardial infarction in 4% and silent ischemia in 1%. The indications for patients with and without β blockers listed in Table I did not differ significantly (p >0.05).

Procedure: PTCA was performed using a steerable guidewire system for all procedures except the first 40, where a fixed guidewire system was used. All procedures were done via the femoral artery. Angiographic success was defined as <50% residual diameter stenosis immediately after PTCA.[17] Procedure success was defined as angiographic success for all lesions attempted in the absence of myocardial infarction, death or emergency coronary bypass grafting during the hospital stay.[17] Follow-up angiograms were recorded, when feasible, 6 months after successful PTCA or earlier if warranted by clinical suspicion of restenosis. Restenosis was defined as a recurrence of a diameter narrowing of more than 50% in the dilated artery segment on a follow-up coronary angiogram.[17]

Medication during and after percutaneous transluminal coronary angioplasty: Treatment with β blockers, calcium antagonists, nitrates and aspirin was continued during and after the procedure. At the start of the procedure, 10,000 IU of heparin was given intravenously followed by repeat intravenous boluses of 5,000 IU hourly for procedures lasting >1 hour. If coronary artery dissection was seen on the immediate postprocedure angiogram and after successful dilation of a total occlusion, continuous intravenous heparin drip was given for ≥24 hours, keeping the activated partial thromboplastin time at 60 to 90 seconds. Table III lists the doses and proportions of the different β blockers used during the follow-up period after successful PTCA in patients undergoing follow-up angiography. Metoprolol in a daily dose of 151 ± 61 mg was the drug most often used (76%), followed by atenolol (14%) and sotalol (4%). In 11 cases (3%) the β-blocking medication was discontinued after 30 ± 18% of the follow-up period, whereas in 357 cases (97%) the medication was continued throughout the follow-up period. Calcium antagonists were used during and after PTCA for 294 of the 426 lesions restudied on follow-up angiograms (69%). In 57 cases (13%) the calcium antagonist was discontinued after 35 ± 17% of the follow-up period. Table IV lists the doses and proportions of the different calcium antagonists. The treatment was combined with calcium antagonists for 250 of the 368 lesions in patients treated

TABLE III Beta Blockers in Patients Having Follow-Up Angiograms After Successful PTCA

	No. (%)	Dose/24-Hour mg Mean ± SD (range)
Metoprolol*	281 (76)	151 ± 61 (50–400)
Atenolol†	52 (14)	86 ± 34 (50–200)
Sotalol	13 (4)	185 ± 68 (80–320)
Others		
Propranolol	5	144 ± 22 (120–160)
Pindolol	5	9 ± 4 (5–15)
Alprenolol‡	1	300
Labetalol	1	800
Combinations§	10	
Sum	22 (6)	
Total	368	

Numbers refer to the number of lesions in patients treated with β blockers during and after successful PTCA. Percentages express the relative proportions of the different β blockers.
* Includes 8 cases where metoprolol was discontinued after 55 ± 43 days (range 24–137 days), which was 25 ± 15% (range 8–55%) of the follow-up period.
† Includes 2 cases where atenolol was discontinued after 55 and 56% (89 and 100 days) of the follow-up period, respectively.
‡ Alprenolol discontinued after 17% (17 days) of the follow-up period.
§ Metoprolol in 9 cases exchanged for atenolol and in 1 case for sotalol after 70 ± 47 days (range 20 to 178 days), which was 46 ± 20% (range 12–87%) of the follow-up period.
SD = standard deviation.

TABLE IV Medication Other than Beta Blockers in Patients Having Follow-Up Angiograms After Successful PTCA

	With β blockers		Without β blockers	
	No. (%)	Dose/24-Hour mg Mean ± SD (range)	No. (%)	Dose/24-Hour mg Mean ± SD (range)
Calcium antagonists				
Nifedipine*	210 (84)†	34 ± 12 (15–80)	18 (41)‡	33 ± 12 (30–80)
Diltiazem*	32 (13)§	202 ± 61 (90–360)	10 (23)	204 ± 64 (120–360)
Verapamil*	6 (2)	227 ± 33 (160–240)	16 (36)‖	390 ± 112 (120–480)
Felodipine*	2 (1)	13 ± 11 (5–20)	0	
Total	250 (68)		44 (76)	
Long-acting nitrates				
NTG mononitrate*	91 (29)	41 ± 6 (20–60)	17 (34)	48 ± 13 (40–80)
NTG*	136 (43)	8 ± 5 (5–39)	20 (40)	16 ± 6 (5–20)
ISDN*	87 (28)	33 ± 23 (15–80)	13 (26)	17 ± 7 (15–40)
Total	314 (85)		50 (86)	
Aspirin	342 (93)	216 ± 116 (125–750)	50 (86)	264 ± 204 (125–750)

* Percentages express the relative proportions of the different calcium antagonists and long-acting nitrates.
† Includes 41 cases where nifedipine was discontinued after 67 ± 33 days (range 8 to 137 days), which was 32 ± 14% (range 6 to 55%) of the follow-up period.
‡ Includes 5 cases where nifedipine was discontinued after 59 ± 19 days (range 35 to 86 days), which was 31 ± 11% (range 15 to 43%) of the follow-up period.
§ Includes 10 cases where diltiazem was discontinued after 92 ± 57 days (range 60 to 196 days), which was 50 ± 22% (range 28 to 90%) of the follow-up period.
‖ Includes 1 case where verapamil was discontinued after 81 days (57% of the follow-up period).
Numbers and percentages refer to the number of lesions after successful PTCA with and without β blockers (368 and 58, respectively).
ISDN = isosorbide dinitrate; NTG = nitroglycerin; other abbreviations as in Table I.

TABLE V Results of PTCA in Patients With and Without Beta Blockers

	With β blockers	Without β blockers	Total
	No. (%)	No. (%)	No. (%)
Angiographic success rate*			
Stenoses	378/459 (82)	66/88 (75)	444/547 (81)
Occlusions	35/65 (54)	4/8 (50)	39/73 (53)
Total	413/524 (79)	70/96 (73)	483/620 (78)
Success procedures†	341/455 (75)	59/86 (69)	400/541 (74)
MI after procedure	16 (3.5)	2 (2.3)	18 (3.3)
Emergency CABG	30 (6.6)	7 (8.1)	37 (6.8)
In-hospital CABG	34 (7.5)	10 (12)	44 (8.1)
Death after procedure	2 (0.4)	1 (1.2)	3 (0.6)
In-hospital death	3 (0.7)	2 (2.3)	5 (0.9)

* Number of successfully dilated lesions/number of lesions attempted.
† Number of procedures with angiographic success for all lesions attempted in the absence of MI, CABG and death.
Abbreviations as in Table I.

TABLE VI Follow-Up and Restenosis Rates in Patients With and Without Beta Blockers

	With β blockers	Without β blockers	Total
	No. (%)	No. (%)	No. (%)
Follow-up rate*	368/413 (89)	58/70 (83)	426/483 (88)
Months to follow-up angiograms			
Mean ± SD	6.5 ± 7.5	8.5 ± 11.6	6.8 ± 8.1
Range	0–71	0–63	0–71
Restenosis rate†			
With CA	97/250 (39)	15/44 (34)	112/294 (38)
Without CA	36/118 (31)	7/14 (50)	43/132 (33)
Total	133/368 (36)	22/58 (38)	155/426 (36)

* Number of lesions with follow-up angiograms/number of lesions successfully dilated.
† Number of lesions with restenosis (diameter narrowing >50%)/number of lesions with follow-up angiograms.
CA = calcium antagonists; other abbreviations as in Table I.

with β blockers (68%), and for 44 of 58 lesions (76%) in patients without β blockers ($p > 0.05$). The treatment rates for long-acting nitrates and aspirin (Table IV) did not differ significantly between the groups with and without β blockers ($p > 0.05$).

Statistical analysis: Unpaired *t* tests were used for continuous variables. For differences in proportions between groups, the critical ratio of difference in proportions (with continuity correction) relative to standard error of difference was used. P values <0.05 were considered statistically significant. Unless otherwise stated, values are mean ± standard deviation.

RESULTS

Coronary angioplasty results in the total population: Success and complication rates for the 541 procedures are listed in Table V. Follow-up angiograms were recorded after 6.8 ± 8.1 months and 426 of the 483 successfully dilated lesions (88%) were restudied (Table VI). The total restenosis rate was 36%, as 155 of 426 lesions had recurred.

Comparison of immediate percutaneous transluminal coronary angioplasty results with and without beta blockers: The success and complication rates (myocardial infarction and emergency coronary artery bypass grafting), listed in Table V, did not differ significantly between the groups ($p > 0.05$), although the β-blocker group tended to have higher success rates. There were 2 deaths in the β-blocker group and 1 in the group without β blockers during emergency bypass surgery after failed PTCA. During the hospital stay there was another death in each group: in the β-blocker group 1 patient died of myocardial infarction occurring 3 days after unsuccessful but otherwise uncomplicated PTCA, and in the group without β blockers 1 patient died suddenly 16 hours after successful and uncomplicated PTCA. The mortality rates did not differ between the groups ($p > 0.05$).

Comparison of restenosis rates with and without beta blockers: The follow-up and restenosis rates are listed in Table VI. The follow-up rates did not differ with or without β blockers ($p > 0.05$). The restenosis rate after treatment with β blockers was 133 of 368 (36%) vs 22 of 58 (38%) without β blockers ($p > 0.05$). Pairwise comparison of the restenosis rates for the 4 subgroups of patients with or without calcium antagonists in the presence or absence of β blockers, listed in Table VI, revealed no significant differences ($p > 0.05$). However, there was a tendency for patients receiving neither β blockers nor calcium antagonists to have a higher restenosis rate than patients receiving either drug or the combination of both.

DISCUSSION

This study evaluates the success and restenosis rates for 541 consecutive PTCA procedures, 455 (86%) in patients treated with β blockers during and after PTCA and 86 (14%) in patients without β blockers. There were no significant differences in success or complication rates with or without β blockers and the restenosis rates did not differ.

Comparison of the groups with and without beta blockers: Treatment with β blockers was common in the study population, 86%, reflecting the strong position of β blockade in our therapeutic tradition for ischemic heart disease. The question arises whether the 14% of the procedures performed without β blockers involve a comparable patient group. The β-blocker group had a higher prevalence of diabetes and a lower proportion of left anterior descending artery dilation (Tables I and II); otherwise, the groups were similar. These factors would affect the restenosis rate in the β-blocker group in opposite directions, because both diabetes[18] and left anterior descending artery involvement[19] are thought to predispose for restenosis. In 56 of 69 patients (81%) the reasons for not using β blockers at the time of PTCA were: previous adverse effects, absence of antianginal effect while receiving treatment with β blockers or satisfactory antianginal effect with other treatment; factors not known to be related to success or restenosis rates. Beta blockers were considered contraindicated in 13 of 69 patients (19%), 2 of whom had congestive heart fail-

ure. Impaired left ventricular function in the absence of overt congestive heart failure was not considered a contraindication for β-blocking treatment. Should the group without β blockers nevertheless be a selection of patients with poor left ventricular function, this would probably decrease the restenosis rate in this group, since an ejection fraction of >50% was found to be a predictor of restenosis in the PTCA Registry of the National Heart, Lung, and Blood Institute.[3] Although the success rates improved and the indications for PTCA widened with time during the period studied, the proportion of patients with and without β blockers did not change significantly, indicating that the groups were not differently selected during different parts of the study period.

Beta blockers during and after arterial injury: Clinical studies of β-blocker treatment after PTCA are lacking. Experimental studies of arterial repair and atherosclerosis after mechanical injury suggest that PTCA induces a complex reparative process.[20] Platelet adhesion and release of α-granule substances may initially be of significance. It has been suggested that β_1-selective blockers, in particular, interfere with this process.[21] Later, smooth muscle cell proliferation appears to take place. Calcium antagonists might blunt the early proliferative response after injury.[11] During later phases of the process lipoprotein deposition in arterial tissue may be of importance. The binding of low-density lipoproteins to arterial tissue is inhibited by β blockers.[22] As β blockers may interfere with ≥2 key elements in the arterial response to injury, it would be logical to extend the medication throughout the follow-up period after PTCA.

Role of beta-adrenergic blockers during and after coronary angioplasty: Intravenous and intracoronary administration of propranolol has been shown to decrease myocardial ischemia during PTCA.[23,24] This speaks in favor of continuing with β-blocker treatment during the procedure. However, concern has been expressed regarding the risk for vasoconstriction and adverse effects on the immediate PTCA results from the unopposed α-adrenergic vasoconstrictor effects during β-blocker treatment.[13] In the present study, no differences in angiographic or procedure success rates were seen with or without β blockers. There was a tendency to higher success rates in the β-blocker group, although not significant. Although we were unable to show any association between β-blocker treatment and a decreased restenosis rate, there was no evidence of any adverse reaction either. Thus, it seems as if the restenosis rate is not affected by β blockers, alone or combined with calcium antagonists. Continued treatment with β blockers after PTCA could accordingly be justified for other indications. The value of β blockade after myocardial infarction is today extremely well documented in close to 50 randomized trials.[25] In our population, 41% of the PTCA patients had sustained a previous myocardial infarction. Furthermore, even after successful PTCA, approximately 33% of the patients within 6 months develop a restenosis (i.e., significant coronary artery disease, symptomatic or silent). Because it is not possible to predict which of the patients with previous myocardial infarction will develop restenosis, continued β blockade in this group seems logical also after successful PTCA.

The antianginal effects of calcium antagonists are well documented,[26] but despite several extensive studies there is no evidence of a secondary preventive effect after myocardial infarction.[27] The most favorable results concern prophylactic diltiazem therapy after non-Q-wave myocardial infarction, where a reduction in the incidence of reinfarction has been proposed.[28] At present, β blockers have a clear advantage over calcium antagonists when secondary prevention after myocardial infarction is considered.

Prevention of restenosis by other drugs: Experimental data suggest that calcium antagonists have a role in preventing restenosis.[11] Despite this, controlled clinical trials of nifedipine[8] and diltiazem[9] have failed to show any reduction in restenosis rates. Our data are in agreement with these studies, because addition of calcium antagonists did not reduce the restenosis rate in either group. A tendency for the patients without both β blockers and calcium antagonists to have the highest restenosis rate has to be viewed with caution because of the small numbers involved. As mentioned earlier, the combination of β blockers and calcium antagonists seems to be theoretically justified during the early phase of the arterial trauma, but again we were unable to show any difference with or without calcium antagonists. Experimental studies suggest roles for many drugs in preventing restenosis. The clinical role of aspirin is debated;[7,10,29] otherwise, none of the drugs tried has been shown to be effective in keeping the restenosis rate below 30 to 35%.[6–10] This can be explained in different ways. As always, translation of experimental results into the clinical situation is unreliable. Intimal hyperplasia appears to be a complex process, involving activity of platelets, growth factors and smooth muscle cells in addition to hemodynamic and mechanical factors.[5,30] To achieve a significant effect on the restenosis rate, drugs with a more directed effect like platelet receptor blockers and antiproliferative agents may be required. In addition to a pharmacologic approach, new technical improvements such as laser angioplasty and stents could have a role in resolving the restenosis problem.

Study limitations: The definitions of angiographic success and restenosis using binary codes with 50% diameter narrowing as the dividing line are not unquestionable, although recommended in the report of the World Health Organization Task Force on Coronary Angioplasty.[17] A differentiated definition might enable the detection of more subtle effects on the development of restenosis. The major limitation obviously is the retrospective design, and a prospective, randomized, placebo-controlled study would be the ideal choice. Another limitation is the inhomogeneity of the medication regimen using different β blockers, although metoprolol dominates (76%). However, because of the cost and effort involved in a major prospective trial, it is questionable whether this is justified considering the results of this study, and the number of other promising drugs waiting to be assessed regarding the effect on restenosis.

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Functional Status After Coronary Artery Bypass Grafting and Percutaneous Transluminal Coronary Angioplasty

Jerilyn K. Allen, ScD, MS, Sheila T. Fitzgerald, PhD, MSN, Robert T. Swank, MA, and Diane M. Becker, ScD, MPH

Two cohorts of consecutive patients of comparable age with similar preprocedure cardiac function who underwent either coronary artery bypass grafting (CABG; n = 106) or percutaneous transluminal coronary angioplasty (PTCA; n = 64) were entered into a prospective comparison study examining functional status and return to work during the first year of recovery. Patients were evaluated using standardized functional status instruments for activities of daily living, work performance, social activity, mental health and quality of social interaction at 1, 6 and 12 months after the procedure. Within the CABG group, statistically significant improvements of functional status on every subscale were noted over the 1-year follow-up. Patients undergoing PTCA demonstrated significant improvement in all dimensions except for the quality of interaction at 1 year as compared with baseline. When the 2 groups were compared, the PTCA group demonstrated greater participation than the CABG group in routine daily physical and social activities at 1 and 6 months, but this apparent advantage disappeared by 1 year. Measures of psychological functioning were better after CABG than after PTCA. A reduction in the number of those with employment occurred in both the CABG and PTCA groups, independent of physical functional status measures, which improved in both groups after the procedures. For those with employment, the CABG group reported the greatest improvement in work performance.

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Improved functional status is a major goal for many patients undergoing coronary artery bypass graft surgery (CABG) and percutaneous transluminal coronary angioplasty (PTCA). Nonrandomized studies comparing these 2 invasive interventions have reported shorter length of hospitalization,[1] lower cost,[2,3] earlier return to work,[4] swifter return of exercise capabilities[4] and better life adaptation[5] in patients undergoing PTCA compared to CABG. The profiles for patients undergoing these procedures have altered considerably in recent years, with a greater number of patients undergoing PTCA for multivessel disease.[6,7] A randomized trial of PTCA versus CABG has not yet been reported in patients with multiple coronary vessel disease and few studies evaluating PTCA and CABG specifically examine the question of actual resumption of usual physical and social activities, subsequent general wellbeing and work performance after these procedures in patients with similar characteristics at baseline. This study was designed to compare functional status outcomes in patients undergoing CABG and PTCA, with similar clinical profiles before intervention.

METHODS

For a 2-year period, 2 cohorts of consecutive patients who underwent either CABG or PTCA at The Johns Hopkins Medical Institutions were entered into comparison studies examining factors predicting functional status and return to work during the first year of recovery. These patients were evaluated by standardized functional status measures before hospital discharge and at 1, 6 and 12 months after the procedure. Patients were ineligible if they had any additional concurrent procedure, previous PTCA or CABG, subsequent CABG or a preprocedure noncardiac disability that limited functional status. Patients >65 years were excluded because of possible age-related functional status impairments and potential work ineligibility. From these 2 cohorts of patients (PTCA = 82; CABG = 125), all patients with complete functional status follow-up assessments were retained for comparison of PTCA versus CABG outcomes. In the resultant sample, the 106 patients in the CABG group and the 64 patients in the PTCA group did not differ significantly in age, preoperative ejection fraction, percentage with a myocardial infarction during the 3 months before the procedure, median length of angina-related disability before the procedure and the percent with Canadian Cardiovascular Society class III

TABLE I Comparison of Sample Characteristics

Sample	Mean Age (yrs)	Mean Preoperative Ejection Fraction (%)	Myocardial Infarction ≤3 Months Before Procedure (%)	Angina Classification III and IV (%)	Median Length Preprocedure Disability (months)	Mean No. of Vessels with Coronary Lesions ≥70%
Patients undergoing CABG (n = 106)	55 ± 7	62 ± 15	69	47	3	2.2 ± 0.9
Patients undergoing PTCA (n = 64)	53 ± 8	62 ± 13	63	48	1.5	1.5 ± 0.7
p Value	NS*	NS*	NS†	NS†	NS*	0.0001†

Differences compared by * Student *t* test for continuous variables and by † cross-tabulation tables and the chi-square statistic for categorical variables. Mean values are ± standard deviation.
CABG = coronary artery bypass grafting; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

or IV angina (Table I). Patients undergoing CABG had significantly more coronary vessels with ≥70% occlusions as compared with those treated with PTCA. Seven of the PTCA patients (11%) underwent repeat PTCA.

Data collection: Functional status was measured by the Beth Israel-University of California at Los Angeles Functional Status Questionnaire,[8] a standardized, validated instrument that provides a reliable comprehensive assessment of physical, psychological, social and work role function. The Functional Status Questionnaire was designed to screen for physical and social disability and to monitor clinically meaningful changes in ambulatory care patients. The Functional Status Questionnaire yields a total summary scale score ranging from 0 to 100. A score of 100 indicates maximum functional ability for each of the following functional status areas: Intermediate Activities of Daily Living, Mental Health, Social Activity, Quality of Social Interaction and Work Performance. Specific items are summarized in the Appendix. Internal consistency of the Functional Status Questionnaire subscales was excellent; α coefficients ranged from 0.71 to 0.99. The same Functional Status Questionnaire was administered by either telephone interview or written questionnaire at the time of hospitalization, and 1, 6 and 12 months after hospital discharge in both patients with PTCA and with CABG. Sociodemographic, myocardial infarction and disease severity data were abstracted from hospital records. Preoperative ejection fraction and number of vessels with ≥70% lesions were determined from the preoperative coronary angiography reports. Length of preprocedure cardiac disability was determined by patient self-report. Anginal severity was classified as I, II, III or IV according to the Canadian Cardiovascular Society Classification for Angina Pectoris.[9] Because ≤50% of the patients in both groups had a treadmill test after the procedure, data on physical functional capacity were not available at follow-up.

Statistical analysis: Paired *t* tests were used to compare patients' functional status at baseline and at 1 year after the procedure within each group. Between-group comparisons on each functional status subscale at baseline, 1, 6 and 12 months after the procedure were completed using the Student *t* test.

RESULTS

Within the CABG group, statistically significant improvements of functional status on every subscale were noted over the 1-year follow-up (Table II). Patients undergoing CABG reported greater participation in usual daily physical activities and social activities, better work performance and improved mental health and interpersonal interactions 1 year after CABG as compared with baseline (the time of CABG). Patients undergoing PTCA displayed significant improvement in daily physical functioning, social activity, work performance and

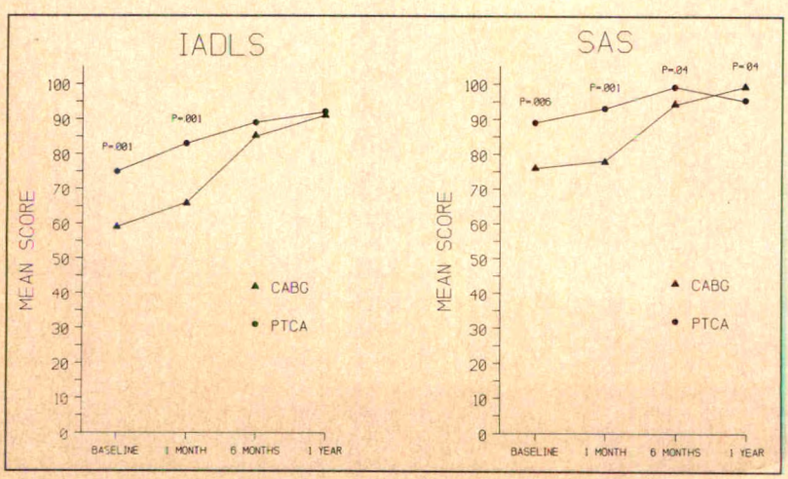


FIGURE 1. Patient scores on the Intermediate Activities of Daily Living (IADLS) and Social Activities (SAS) Subscales of the Functional Status Questionnaire after coronary artery bypass graft surgery (CABG) or after percutaneous transluminal coronary angioplasty (PTCA).

mental health in the 1 year of follow-up. Quality of interaction scores were high in the PTCA group at baseline and remained so 1 year later.

Physical and social functional status: At baseline, and 1 month after the procedure, PTCA patients demonstrated significantly better reported functioning in physical activities of daily living ($p = 0.001$) and social activities ($p = 0.006$) than CABG patients (Figure 1). By 6 months after the procedure, CABG patients began to approximate physical and social functional status levels reported by PTCA patients. At 1 year of follow-up, self-reported participation in the physical activities of daily living was similar in both groups, while self-reported social functional status scores were significantly higher in the CABG group than in the PTCA group ($p = 0.04$). Self-reported levels of social and daily functioning activities began higher in PTCA patients and improved only slightly over the 1-year follow-up period, whereas levels of these activities were lower in CABG patients at baseline and improved significantly over the 1 year of follow-up.

Psychological functional status: PTCA patients' estimates of their mental health and quality of interaction were better but not significantly different from those of patients in the CABG group before undergoing the procedure (Figure 2). At 1 month the pattern of psychological functioning changed. Patients in the CABG group estimated their mental health ($p = 0.08$) and quality of interaction ($p = 0.02$) to be better than those in the PTCA group. This pattern of psychological functioning continued at 6 months and 1 year after the respective procedures.

Work performance: The percentages of patients employed fulltime before and after CABG and PTCA were very similar (Table III). The percentage employed 1 year after the procedure decreased slightly from before the procedure in both groups.

For those working in each group, estimates of work performance during the month before the procedures did not differ (Table III). At 6 months, the 61% of employed patients in the CABG group had significantly higher work performance scores than the 73% of employed patients in the PTCA group, 95 versus 86 ($p = 0.003$). The trend of better work performance scores in the CABG group continued at 1 year.

The 7 patients in the PTCA group who underwent a second angioplasty did not differ significantly on any functional status outcomes from the 57 PTCA patients who did not undergo an additional procedure.

TABLE II Functional Status in Patients Undergoing CABG and PTCA: Comparison of Baseline and One-Year Follow-Up Scores Within Groups

FSQ Subscale	Time: Mean Score One Month Before the Procedure	Time: Mean Score One Year After the Procedure	Paired *t* Test p Value
CABG (n = 106)			
Physical activity	59 ± 25	91 ± 14	0.0001
Social activity	76 ± 35	99 ± 5	0.0001
Work performance	81 ± 24	93 ± 11	0.0004
Mental health	61 ± 23	82 ± 14	0.0001
Quality of interaction	77 ± 16	84 ± 13	0.0002
PTCA (n = 64)			
Physical activity	75 ± 26	92 ± 18	0.0001
Social activity	89 ± 24	95 ± 17	0.03
Work performance	79 ± 23	89 ± 17	0.003
Mental health	67 ± 19	77 ± 17	0.0001
Quality of interaction	80 ± 13	80 ± 13	0.95

FSQ = Functional Status Questionnaire; other abbreviations as in Table I. Mean scores are ± standard deviation.

DISCUSSION

Findings indicate that patients of comparable age with similar cardiac function before the procedure who undergo CABG or PTCA report some differences in functional status during the first year of recovery. The PTCA group demonstrated greater participation in routine daily physical and social activities than the CABG group at 1 and 6 months. However, this apparent advantage of PTCA disappeared by 1 year. Initial differences may be largely attributed to the longer postoperative recovery required of patients who undergo CABG.

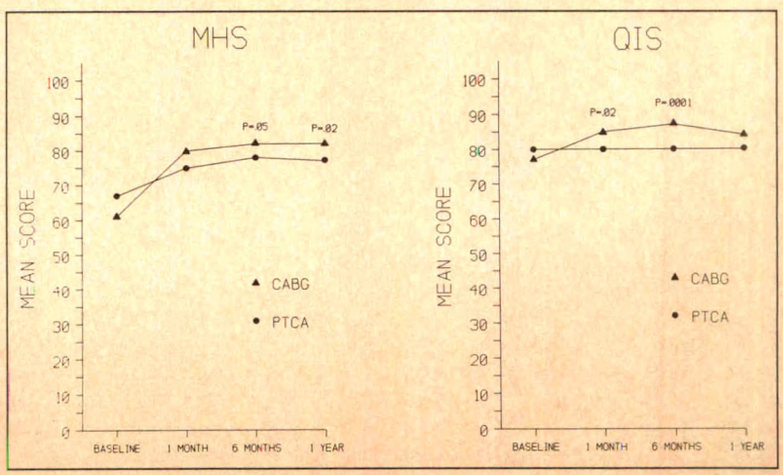


FIGURE 2. Patient scores on the Mental Health (MHS) and Qualtiy of Interaction (QIs) Subscales of the Functional Status Questionnaire after cornary artery bypass graft surgery (CABG) or after percutaneous transluminal coronary angioplasty

TABLE III Percentage of Full-Time Employment and Ratings of Work Performance Before and After Procedure in Patients Who Underwent CABG and PTCA

	Time					
	Six Months Before Procedure		Six Months After Procedure		One Year After Procedure	
Procedure	% Employed	Mean ± SD*	% Employed	Mean ± SD*	% Employed	Mean ± SD*
CABG (n = 106)	75	81 ± 24	61	95 ± 9†	71	93 ± 11
PTCA (n = 64)	72	79 ± 23	73	86 ± 20	70	89 ± 17

* Self-Reported Work Performance Score on Functional Status Questionnaire.
† p = 0.003.
Abbreviations as in Table I.

APPENDIX

Functional Status Questionnaire

Subscale	Item
	During the past month have you had difficulty:
Intermediate ADL	Walking several blocks?
	Walking 1 block or climbing 1 flight of stairs?
	Doing work around the house, such as cleaning, light yard work, home maintenance?
	Driving a car or using public transportation?
	Doing vigorous activities such as running, lifting heavy objects, participating in strenuous sports?
Social activity	Visiting with friends and relatives?
	Participating in community activities such as religious services, social activities or volunteer work?
Responses: usually did with no difficulty (4), some difficulty (3), much difficulty (2), usually did not do because of health (1), usually did not do for other reasons (0).	
	During the past month:
Mental health	Have you been a very nervous person?
	Have you felt calm and peaceful?*
	Have you felt downhearted and blue?
	Were you a happy person?*
	Did you feel so down in the dumps that nothing could cheer you up?
Quality of interaction	Isolated yourself from people around you?
	Acted affectionate toward others?
	Acted irritable toward those around you?
	Made unreasonable demands on your family and friends?
	Gotten along well with other people?*
Responses: all of the time (1), most of the time (2), a good bit of the time (3), some of the time (4), a little of the time (5), none of the time (6).	
Work performance (for those employed)	
	Done as much work as others in similar jobs?*
	Worked for short periods of time or taken frequent rests because of your health?
	Worked your regular number of hours?*
	Done your job carefully and accurately as others with similar jobs?*
	Worked at your usual job, but with some changes because of your health?
	Feared losing your job because of your health?
Responses: usually did with no difficulty (4), some difficulty (3), much difficulty (2), usually did not do because of health (1), usually did not do for other reasons (0).	

* Reverse scored items. ADL = activities of daily living.

Measures of psychological functioning (general mental health and quality of social interaction) indicated better functioning after CABG than after PTCA. This finding appears counterintuitive given the length and complexity of recovery after CABG as compared with PTCA. However, patients who undergo PTCA are often told that they should be capable of returning to normal activities within 1 or 2 weeks. These expectations are often unrealized and the discrepancy between expectations and reality may cause depression or anxiety. Patients' concerns about reocclusion may also contribute to poorer psychological functioning. Patients may not perceive PTCA to be as minimally invasive as the clinical community does.[10] Patients undergoing CABG may have more realistic expectations and may be able to attribute symptom recurrences to the surgical recovery.

At baseline, both groups reported comparable work performance. The PTCA group demonstrated an upward but not significant improvement on this scale after PTCA. This may reflect the fact that there is minimal physical recovery involved after PTCA as well as the fact that patients who are working before PTCA do not expect a change in their work performance after PTCA. The CABG group, however, showed greatest improvement in reported work performance between baseline

and follow-up at 6 months, which parallels recovery after CABG and reflects improved overall functional status.

Studies have consistently shown that return to work after CABG[11] and PTCA is less frequent than would be expected from the significant improvements observed in physical functional status and relief of anginal symptoms. This study demonstrated that there was no net improvement in work resumption for either PTCA or CABG patients.

The prevalence of chest discomfort varied in the 2 populations during the 12 months of recovery. As expected, a higher percentage of the CABG patients (81%) reported chest discomfort at 1 month when compared to PTCA patients (56%). Over time, fewer CABG patients (6 months = 48%; 1 year = 32%) and more PTCA patients (6 months = 63%; 1 year = 60%) reported some degree of chest pain. Whether this chest pain could be attributed to changes in coronary blood flow cannot be determined. Recurrence of chest discomfort and its impact on perceptions of ability remains a potential explanatory variable that cannot be answered in this study.

The results of this study differ from the previous findings of Raft et al[5], who showed that scores on some subscales of the Psychosocial Adjustment to Illness Scale for patients who had undergone PTCA were significantly better than the scores for those who had undergone CABG at 6 and 15 months after the procedure. However, that study was comprised of a small sample (n = 32) who underwent these procedures 7 years ago, when patients selected for PTCA had generally less severe coronary artery disease and were younger.

This study compared functional status outcomes in patients of comparable age with similar cardiac function before the procedure who underwent either CABG or PTCA. Advantages in some functional status dimensions demonstrated in the CABG population cannot be explained by better physical status at baseline, as these patients had more multivessel disease than did those with PTCA. The findings suggest that by 1 year, CABG patients are functioning as well or better than PTCA patients. Clinicians should be aware of functional status dimensions of recovery from both procedures as well as the traditional morbidity and mortality outcomes.

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Patient-Related Variables and Restenosis After Percutaneous Transluminal Coronary Angioplasty — A Report from The M-HEART Group

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As part of a randomized prospective study designed to investigate the restenosis process after percutaneous transluminal coronary angioplasty (PTCA), the relation between patient-related variables and restenosis rate was examined. A total of 722 patients had successful PTCA. Angiographic follow-up was scheduled for 6 ± 2 months after the procedure and achieved in 510 patients (71%), yielding 598 lesions for analysis. The overall restenosis rate was 40%. The rate was higher in patients undergoing early restudy for a clinical event than in those undergoing routinely scheduled follow-up restudy (71 vs 22%, p <0.0001). Age, sex, cigarette smoking history, diabetes mellitus and history of previous myocardial infarction were not associated with restenosis rate. Angina duration and severity before PTCA were also unrelated to restenosis rate. In summary, these variables, many of which have been previously implicated in restenosis, were not found to be predictors of restenosis. The decision to perform PTCA in individual patients should not be negatively influenced by the presence of these factors.

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Coronary restenosis continues to be a major problem after percutaneous transluminal coronary angioplasty (PTCA). The reported incidence at 6 months after PTCA ranges from 17 to 47%. Previous studies have identified a variety of procedural and patient-related variables that may be associated with increased restenosis rates.[1–26] These have generally been single-center retrospective analyses and not prospective studies specifically designed to evaluate risk factors for restenosis. Although many procedural variables are generally accepted as predictors of restenosis, an association with patient-related variables has not been consistently demonstrated. As part of a multicenter trial, we prospectively analyzed the relation of various lesion, procedural and patient-related variables to restenosis. This report examines whether patient-related variables influence the rate of restenosis after PTCA.

METHODS

The Multi-Hospital Eastern Atlantic Restenosis Trial study group (M-HEART; centers and investigators are listed in the Appendix) was established in 1985 to investigate the restenosis process and the influence of various pharmacologic or procedural modifications on restenosis.

The initial interventional phase of this study involved evaluation of the effect of glucocorticoid administration on the restenosis process. Details and results of this aspect of the study are described elsewhere.[27] Briefly, entry criteria were: the presence of ≥1 coronary stenosis ≥60% (diameter reduction); all ages; either gender; willingness to sign an informed consent and to undergo angiographic restudy; and absence of the exclusion criteria. Exclusion criteria were: PTCA performed to revascularize acute myocardial infarction (<12 hours); contraindication to steroids; anticipated need for steroids within the next 6 months; administration of corticosteroid or other immunosuppressive drugs during the previous 30 days and renal failure (creatinine >3.0 mg/dl). Patients with PTCA of total occlusion, bypass grafts and restenosis lesions were not excluded. Initial patient evaluation included a history and physical examination, a resting and exercise electrocardiogram (if

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*See Appendix for contributing centers and investigators.

clinically indicated) and cardiac catheterization with left ventricular and selective coronary angiography. All data were prospectively entered into a standardized form and forwarded to the data coordinating center for storage in an IBM 4381 mainframe computer using the FOCUS database management system and SAS statistical software package.

Historical data: Patient age, sex, history of diabetes mellitus, cigarette smoking, previous myocardial infarction, variant angina, and duration and severity of angina were documented.

Angiographic data: Coronary angiography before PTCA and at follow-up was performed after administration of nitroglycerin. An attempt was made to demonstrate the stenosis in orthogonal views. Coronary artery and stenosis diameters and percent stenosis were obtained by handheld caliper measurements from the projected cineangiogram without knowledge of clinical variables or treatment assignment. The diameters of nonstenosed segments were determined by averaging measurements from segments just proximal and distal to the stenosis. Percent coronary stenosis (diameter reduction) was obtained from the single view showing the most severe narrowing. Measurements were obtained in a similar fashion from an identical angiographic view after PTCA. A successful PTCA was defined by a final stenosis of <50% associated with clinical benefit and no major complications.

Study protocol: The study protocol is illustrated in Figure 1.

Percutaneous transluminal coronary angioplasty procedure: PTCA was performed from either the femoral or brachial approach. Intravenous heparin (10,000 to 12,000 units) was administered at the start of the procedure and supplemented in longer cases. Intravenous or intracoronary nitroglycerin was given during the procedure. Selection of PTCA balloon size was based on the diameter of the nonstenosed segment from the pre-PTCA angiogram, seeking an inflated balloon to coronary diameter ratio of 1.0. At least 1 balloon inflation was to be ≥6 atmospheres pressure for ≥60 seconds, if tolerated. The procedure was terminated when an optimal angiographic and hemodynamic result was obtained. A final transstenotic gradient of <15 mm Hg, when measured, and a visually estimated percent stenosis <25 were considered optimal.

Medications: BEFORE PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY: Aspirin (325 mg/day) was started >24 hours before PTCA. Antianginal agents (calcium antagonists, long-acting nitrates, β adrenergic blockers) were used as single or combination agents as clinically indicated.

AFTER PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY: After successful PTCA, an effort was made to taper and eliminate all antianginal medications by 4 weeks after the procedure, unless other indications for use were present. Aspirin was continued until a study end point was reached.

Experimental therapy: Either methylprednisolone (1 g) or placebo was given as a single intravenous bolus 2 to 24 hours before PTCA, according to a randomization schedule generated at the coordinating center for each clinical site.

Follow-up: A follow-up coronary angiogram was scheduled for 6 months after PTCA but performed earlier if a clinical event occurred. A clinical event was defined as development of symptoms or signs of myocardial ischemia, myocardial infarction or sudden death. Angiography performed for evaluation of a clinical event that showed no evidence of restenosis was accepted as "qualifying data" only if performed >4 months after PTCA.

Restenosis was defined as a narrowing >50% at the site of previous dilation measured from the same angiographic view as before and immediately after PTCA.

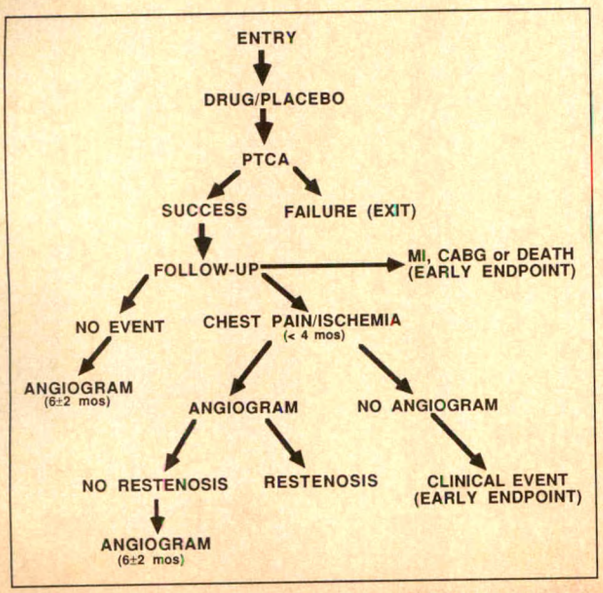


FIGURE 1. Study protocol. After successful PTCA, patients were routinely scheduled to return 6 months later for follow-up coronary angiography. If a clinical event occurred, angiography was performed as soon as practical. If restenosis was not present and time of angiography was <3 months from date of PTCA, the initially scheduled routine follow-up angiography was later performed. CABG = coronary artery bypass grafting; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

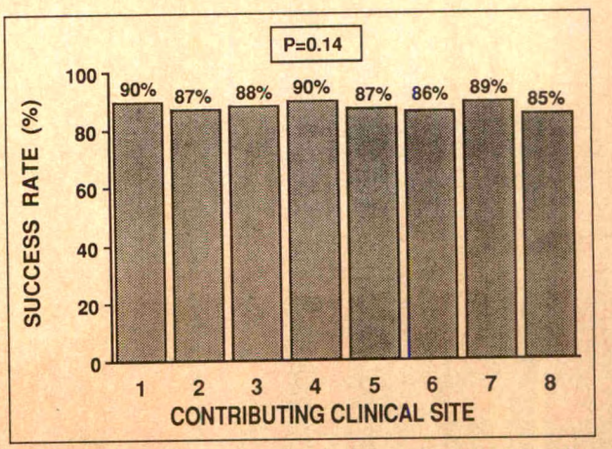


FIGURE 2. Success rate by contributing clinical site. The primary success rate in the study averaged 88%. The range, from 85 to 90%, indicates comparability among participating sites in this multicenter study.

TABLE I Restenosis Rate by Demographic Variables

Variables	Restenosis Rate No.	Restenosis Rate (%)	p Value
Sex			
Female	48	42	0.55
Male	189	39	
Age (yrs)			
30–50	69	45	0.09
51–58	49	35	
58–65	51	34	
>65	68	44	

Study end points: End points for this study included initially unsuccessful PTCA, early occurrence of a clinical event, documented restenosis or completion of >4 months follow-up with an angiogram showing no restenosis.

Data analysis: Restenosis rate was expressed as a percentage of all stenoses successfully dilated and restudied. The restenosis rate was separately determined for the total patient population restudied, patients having early angiographic follow-up for a clinical event, and those undergoing routinely scheduled restudy. For the entire group restudied, data were analyzed to determine whether there was an association between restenosis rate and any patient-related variables recorded at entry. Statistical significance of these associations was tested by any of several univariate analyses as appropriate. For continuous variables, *t* tests were used and for discrete variables, chi-square analyses were done. A p value <0.05 was considered significant.

RESULTS

Primary success and restudy rate: PTCA was successfully performed in 722 of 826 patients attempted—a primary success rate of 87%—and there were no significant differences between sites (Figure 2). There were also no differences between sites relative to complication rates and need for emergency coronary bypass surgery. In total, 886 of 1,000 lesions (89%) were successfully dilated. Angiographic follow-up within the defined time period was achieved in 71% of patients, yielding 510 patients with 598 lesions for analysis. Of these, 333 patients (65%) had restudy as routinely scheduled and 177 (35%) had earlier angiography for a clinical event. Of the patients not restudied, 28 had criteria for early end points: 15 died, 7 had early coronary artery bypass surgery and 6 had early restudy (<4 months) without restenosis and refused second restudy. These 28 were not included in the analysis.

Restenosis: Of the restudy population, restenosis occurred in 237 of 598 arteries dilated (40%). In patients undergoing early restudy because of a clinical event, the rate was 71%. This was significantly higher in those undergoing routine angiographic follow-up (22%, p <0.0001).

Patient-related variables: AGE AND SEX: There was no statistically significant relation between restenosis and age when analyzed either as a continuous variable or by specific age groups (Table I). The mean age of patients having successful PTCA was 59 years, with a range of 32 to 86 years. Of the population restudied after successful PTCA, 103 of 510 patients (20%) were women. The restenosis rate in women was slightly higher than in men but this difference was not statistically significant (Table I).

SMOKING: There was no significant relation between restenosis and smoking (Figure 3). This was analyzed in 2 ways: by those smoking at the time of PTCA and by those who had resumed or continued smoking at the time of restudy. At the time of PTCA, 26% of patients were smokers. The restenosis rate for smokers (37%) compared with nonsmokers (42%) was not significantly different. At restudy, there were 24% fewer smokers.

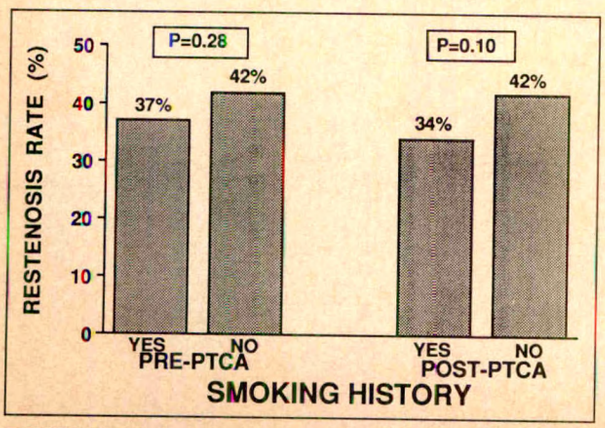


FIGURE 3. Effect of smoking on restenosis rate. At the time of PTCA (pre-PTCA) 26% of patients had a history of current smoking. There were 24% fewer smokers at the time of restudy (post-PTCA). Differences in restenosis rates were not significant.

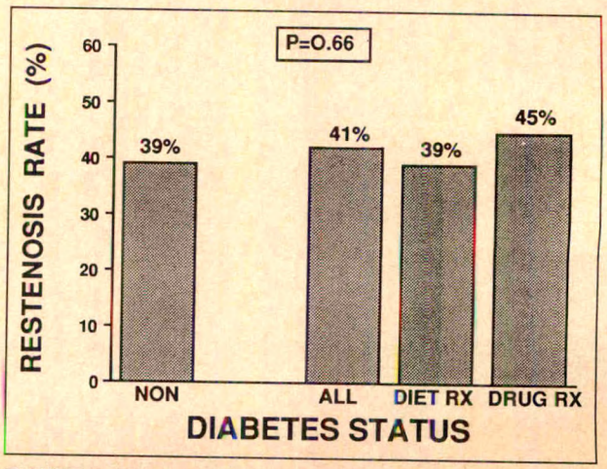


FIGURE 4. Effect of diabetes on restenosis rate. There were relatively few diabetics in this study (75 dilated arteries for analysis). The restenosis rate in diabetics, whether treated with diet alone or requiring hypoglycemic therapy, was not significantly different from nondiabetics. non = nondiabetes; Rx = therapy.

For patients who continued to smoke, the restenosis rate was not significantly different compared with nonsmokers.

DIABETES: The relation between diabetes and restenosis rate is shown in Figure 4. There were relatively few diabetics in this study. Of the 510 patients undergoing restudy, 60 had diabetes, yielding 75 dilated arteries for analysis. Only 18 of these arteries were in insulin-dependent diabetics; 31 were from patients receiving oral agents. The restenosis rate was not significantly higher in diabetics. The rates in diabetics requiring drug therapy were also not significantly different from those in nondiabetics. Thus, diabetes, whether controlled by diet or requiring hypoglycemic therapy, was not associated with higher restenosis rates.

PREVIOUS MYOCARDIAL INFARCTION: Of the total population of lesions for analysis, 143 (24%) were from patients with previous myocardial infarction. Of these, 55 (38%) subsequently restenosed (Figure 5). This compares with a restenosis rate of 40% for patients without previous myocardial infarction (difference not significant).

SEVERITY AND DURATION OF ANGINA: The relation between duration and severity of angina and restenosis rate are shown in Figures 5 and 6, respectively. There were relatively few patients with class I angina undergoing PTCA (7% of all patients restudied). Patients with class IV angina, or angina at rest, did not have higher restenosis rates. In fact, the restenosis rates for the different functional classes were remarkably similar (39 to 40%). Just over half of patients (55%) had angina of >3 months duration. The restenosis rate in this group was 39%, versus 43% in patients with more recent onset of angina ($p = 0.3$).

CORONARY SPASM: Only 4 patients had evidence for coronary spasm before PTCA. Of these, only 1 developed restenosis.

DISCUSSION

Methodology considerations: The primary success and angiographic restudy rates compare favorably to previous studies. The restenosis rate reported for the total patient population in this study was higher than in some reports. This may relate to the definitions used or selection bias associated with incomplete angiographic follow-up and the tendency for more symptomatic patients (those with greater likelihood of restenosis) to return for follow-up angiography. Although consent for follow-up angiography was obtained from all patients before entry, it is obviously impossible to enforce their return for restudy. Nonetheless, this overall high restenosis rate should not introduce bias into data obtained pertaining to the association between patient-related variables and restenosis rate. This is particularly true given that the distribution of these variables in patients with and without restudy was similar. In this study, there was no overall effect of glucocorticosteroids on restenosis, so separate analysis of variables according to treatment assignment is not necessary.

The results of this study contradict data from many reports where associations between patient-related variables and restenosis are described.[1-10] However, no previous similar study has been prospectively designed to address specific patient-related variables as risk factors for restenosis. Our data were prospectively collected as part of a major multicenter trial designed to evaluate many variables associated with restenosis and the question of whether glucocorticosteroids influence the restenosis rate. However, extensive analysis of individual variables, such as quantitating amount smoked, or adequacy of serum glucose control in diabetes, was not possible. In addition, there were relatively few diabetics in this study, in part due to the relative contraindication for steroid administration in diabetics with "brittle" blood sugar control. A larger population of diabetics may have demonstrated different results.

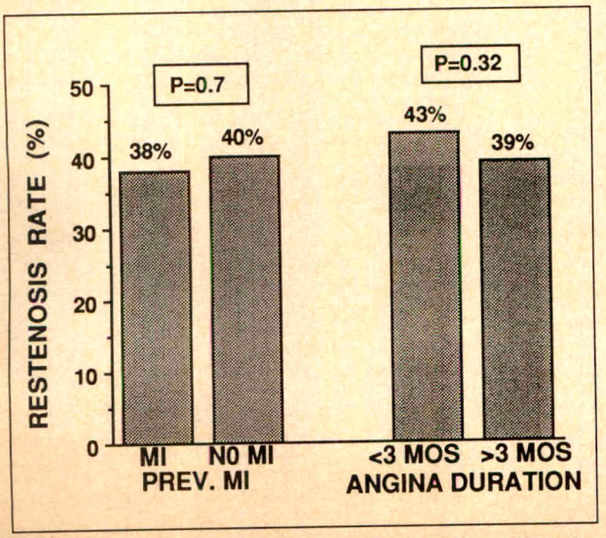


FIGURE 5. Effect of previous myocardial infarction (MI) and duration of angina on restenosis rate. Only 24% of patients had had a previous MI. Neither variable had a significant effect on restenosis. PREV. = previous.

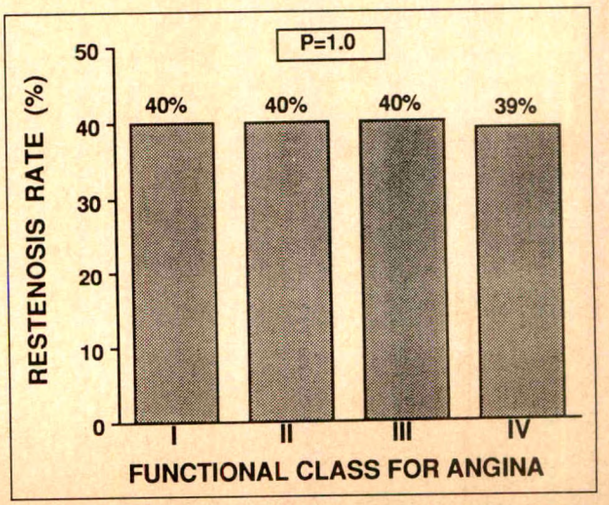


FIGURE 6. Relation between severity of angina before PTCA and restenosis. Only 6.5% of patients had functional class I angina as assessed by Canadian Cardiovascular Society classification.

The low prevalence of patients with coronary artery spasm in this study reflects 2 considerations: first, ergonovine testing was not done routinely before and after PTCA to test for coronary spasm, although most of our centers frequently perform ergonovine testing when there is a clinical suspicion that coronary spasm is part of the patient's presenting chest pain syndrome. Second, in patients with suspected or proven coronary spasm there was a strong tendency to avoid PTCA in view of previous studies showing high acute complication and restenosis rates.[22–26]

Traditionally, it has been thought that patient-related factors that predispose to atherosclerosis are also risk factors for restenosis after PTCA. Surprisingly, age, male sex, smoking and diabetes were not associated with restenosis. Because of the difficulty of providing a stable diet, and the observation that the need for PTCA prompts many patients to undergo diet or lipid medication changes, lipids were not routinely measured prospectively. Although some of the atherogenic factors analyzed in this study may be important determinants of long-term patency of coronary bypass grafts or coronary artery disease progression, we failed to demonstrate any influence on the process of coronary restenosis, at least in the short term. This is not surprising in view of histologic evidence from postmortem and atherectomy specimens from restenosis lesions demonstrating fibrocellular material rather than atheroma.[28–31] Whether these patient-related factors are important in longer-term (e.g., 5-year) patency of the dilated segment remains to be addressed.

In selecting individual patients for PTCA, it is important to consider not only the potential primary success and complications of the procedure but also long-term response and hence likelihood of restenosis. The results of this study suggest that none of the patient-related variables analyzed is an important predictor of restenosis. The presence of these variables, therefore, should not have a negative influence on the decision to perform PTCA in individual patients.

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APPENDIX
M-HEART Study Group

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Results of Percutaneous Transluminal Coronary Angioplasty of High-Risk Angulated Stenoses

Stephen G. Ellis, MD, and Eric J. Topol, MD

Percutaneous transluminal coronary angioplasty (PTCA) of angulated stenoses has been found in studies using older PTCA equipment to be associated with a heightened risk of procedure-related major ischemic events. To better understand the factors associated with procedural risk and to identify means of lessening that risk, 100 patients, treated sequentially from 1986 to 1989, who underwent PTCA of stenoses located at ≥45° bends, were characterized for 27 clinical, anatomic and procedural variables. Clinical outcome of angioplasty was related to these variables. In addition, results from 344 consecutive contemporary patients undergoing PTCA of nonangulated lesions were compared to those of the study group. Procedural success was achieved in only 70% of patients with angulated stenoses, compared with 306 of 344 (89%) nonangulated stenoses, and major ischemic complications (death, bypass surgery or myocardial infarction) occurred in 13% of patients with angulated stenoses compared with 12 of 344 (3.5%) with nonangulated stenoses (both p <0.001). The presence of associated thrombus, stenosis length >10 mm or age ≥65 years led to an even higher risk of major complications (9 of 44 = 20.5%), whereas highly experienced angioplasty operators and the use of polyethylene terephthalate balloons appeared to decrease risk and increase the likelihood of success. PTCA of such stenoses should be undertaken only cautiously and in carefully selected patients.

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It is well recognized that flow disturbances associated with changes in artery direction predispose to atheroma formation[1] and perhaps as many as 12% of all ≥50% stenoses occur in areas of vessel angulation ≥45°.[2] Percutaneous transluminal coronary angioplasty (PTCA) of such stenoses is known to be associated with a heightened risk of ischemic complications, estimated to be 10 to 13% from available series,[3,4] owing to an increased likelihood of arterial tearing (dissection). In fact, vessel angulation may contribute to as many as 44% of all major ischemic complications of coronary angioplasty.[4] Analyses of clinical, anatomic and procedural variables associated with adverse PTCA outcome in this setting are not available. Therefore, 100 consecutive patients with PTCA performed at sites of ≥45° angulation were extensively characterized to gain insight into how best to manage patients in this high-risk setting.

METHODS

Patient population: Every third coronary angioplasty performed in the setting of stable or unstable angina pectoris from March 1986 to June 1989 was reviewed by an experienced angiographer unaware of the outcome of the procedure to ascertain if the first angioplasty had been performed to a stenosis in which the inflated balloon extended across a ≥45° arterial bend (present at end-diastole in a nonforeshortened view).[4] One hundred of 444 patients met this criteria and formed the study population. The remaining 344 had a non-infarct and a nonangulated artery dilated during this time period, and the first stenosis dilated in this group comprised a control population.

Angioplasty procedure: The technique of angioplasty used has been described elsewhere.[5] All patients were pretreated with oral aspirin 80 to 650 mg daily for a minimum of 24 hours. After the administration of heparin (10,000 U intravenous bolus) and sometimes of nitroglycerin (0.4 mg sublingual), preliminary angiography of the coronary artery to be dilated was performed in at least 2 projections. A dilatation balloon was chosen to have its inflated diameter approximate the normal lumen diameter at the site to be dilated. The balloon was positioned across the stenosis and inflated as many times as necessary to produce an optimal angiographic result. That result was angiographically documented in ≥1 projection best showing the stenosis. Sheaths were usually removed 3 to 4 hours after completion of the procedure unless angiographic evidence of a coronary dissection or thrombus was seen, in which case an intravenous infusion of heparin (usually 1,000 U/hour ad-

justed to the partial thromboplastin time) was administered overnight. After PTCA, the patients were taken to a postprocedure ward or to an intensive care unit, where they were monitored for a minimum of 18 to 24 hours. The patients were medicated with aspirin and a calcium antagonist, or nitrate preparation, or both. A 12-lead electrocardiogram was obtained immediately in the event of chest pain suggestive of ischemia, and, if ischemia was suspected, patients were usually returned for a cardiac catheterization and creatine kinase levels were followed. The patients were routinely discharged 1 to 2 days after PTCA.

Variables assessed: The following variables were assessed in the study group. Clinical variables were age, current smoking, gender and unstable angina pectoris. Anatomic variables were number of class B American College of Cardiology/American Heart Association (ACC/AHA) lesion characteristics,[6] active stenosis angle, stenosis angle at end-diastole (Figure 1), asymmetric stenosis, bifurcation stenosis, calcification, chronic total occlusion, lesion length ≥50% (to the nearest mm), multivessel disease, ostial stenosis, percent diameter stenosis before PTCA, roughened stenosis contour, thrombus and vessel tortuosity. Procedural variables were maximum balloon pressure, maximum balloon inflation duration, number of balloon inflations, maximum dilated balloon:artery ratio, experienced angioplasty operator (≥500 procedures performed), use of dilatation balloon containing polyethylene terephthalate material (when multiple balloons were used, the balloon that completed an uncomplicated procedure, or that which was used immediately before vessel disruption or closure, was entered for analysis) and initial dilatation to ≤5 atm. The definitions of these characteristics have been described previously.[4,7] The presence or absence of an angioplasty-induced tear (intimal disruptions ≤2 mm that did not impair coronary flow were excluded) was noted in all study group patients and in a randomly selected subpopulation (n = 100) of the control group (Figure 2). All observations were made by an experienced angiographer unaware of clinical outcome. Dimensional measurements were made using a handheld caliper system and guide catheter calibration. The control population was characterized with regard to age, the presence of unstable angina, the vessel dilated and percent stenosis before PTCA.

Definitions of procedural success and complications: Procedural success was defined as reduction of the stenosis dilated to <50% diameter stenosis and the absence of major ischemic complications through the time of hospital discharge. Major ischemic complications were defined as procedure-induced ischemia leading to death, bypass surgery or myocardial infarction (creatine kinase >2 times upper limit of normal with MB fraction >4%).

Statistical analysis: Data are expressed as mean ± 1 standard deviation unless otherwise indicated. Chi-square analyses were used to test differences in categorical variables, whereas unpaired Student *t* tests were used to assess differences in continuous variables. Multiple stepwise logistic regression analyses were performed to determine clinical, angiographic and procedural correlates of outcome. The variable "angioplasty-induced tear" was considered a result of the procedure and therefore was not included in these analyses. All analyses were performed using SYSTAT software.[8]

RESULTS

Patient characteristics: Characteristics of the patients in the study population are listed in Table I. Patients in the study population did not differ from those having a nonangulated artery dilated in age (60 ± 10 vs 59 ± 9 years), incidence of unstable angina (42 vs 38%), percent diameter stenosis before PTCA (73 ± 11 vs 69 ± 12%) or the distribution of vessels dilated (left anterior descending artery = 31%, left circumflex artery = 31%, right coronary artery = 31%, saphenous vein bypass graft = 7% in the study group vs 33, 28, 33 and 5%, respectively, in the control group.)

Success and complications: Procedural success was achieved in only 70 of 100 (70%) of the study patients compared with 306 of 344 (89%) in the control group ($p < 0.001$). Major ischemic complications occurred in 13 of 100 (13%) of the study patients, compared with 12 of 344 (3.5%) of the control patients ($p < 0.001$). An angioplasty-induced tear was evident in 46% of the study group and 8% of the control group ($p < 0.001$), and the presence of a tear in the study group was correlated with the occurrence of a major ischemic event (20% in-

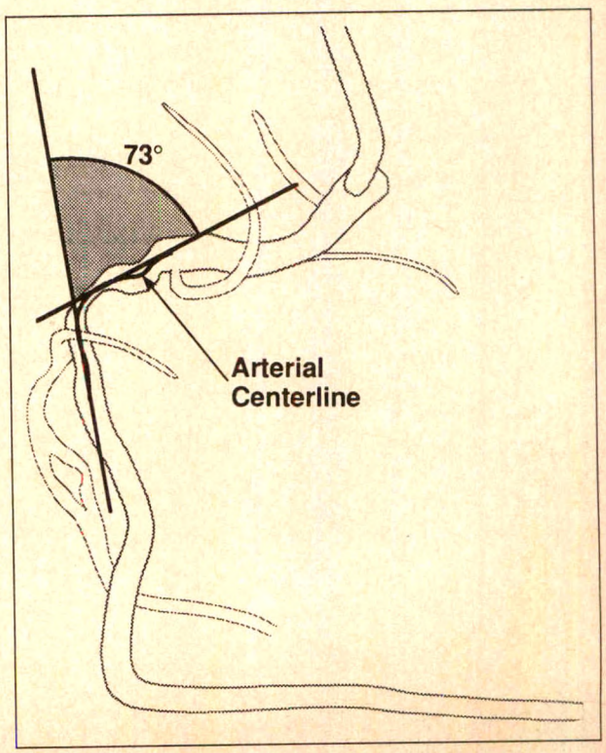


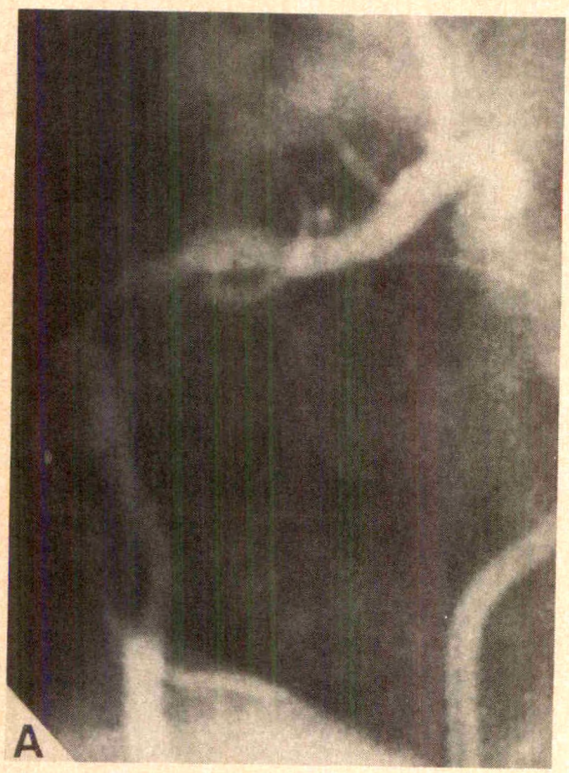
FIGURE 1. Method of angle measurement. In a nonforeshortened end-diastolic projection, the arterial centerline is drawn for a 20-mm segment centered on the stenosis. The angle between the proximal and distal segments is measured.

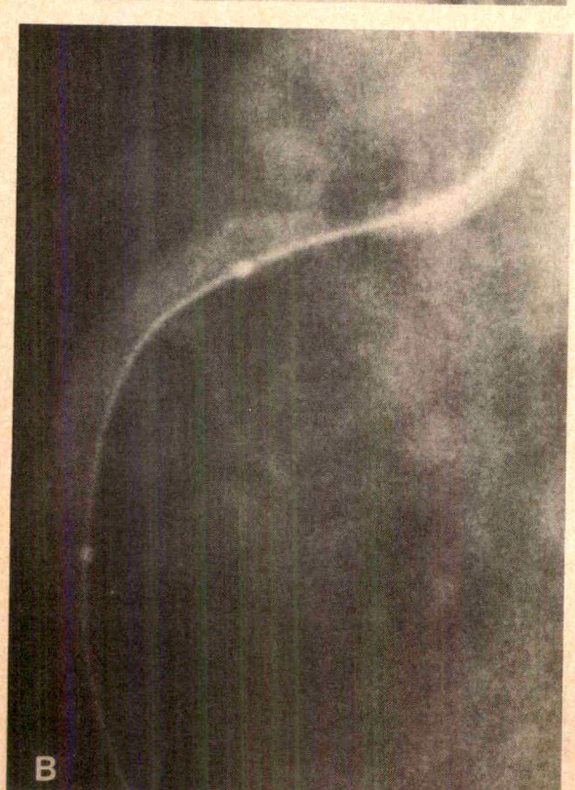
cidence with a tear vs 7% incidence without a tear, p = 0.07). Reasons for procedural failure in the study population were the following: failure to dilate to a <50% stenosis, discharged with medical therapy (11 patients, of whom 6 had a tear), angioplasty-induced ischemia requiring emergency bypass surgery (n = 8), failure to dilate to a <50% stenosis with elective bypass surgery (n = 4), failure to cross the stenosis with the dilatation balloon with subsequent elective bypass surgery (n = 3), failure to cross the stenosis with the guidewire with subsequent elective bypass surgery (n = 1), failure to cross the stenosis with the guidewire, and discharged treated with medical therapy (n = 1), angioplasty-induced ischemia leading to cardiac death (n = 1) and guidewire-induced dissection treated with elective bypass surgery (n = 1).

Correlates of procedural success and major ischemic complications: The correlates of angioplasty success and complications are listed in Tables II and III. The relation of the balloon dilatation catheter type to procedural outcome is listed in Table IV. Interestingly, highly angulated (≥60°) stenoses did not have a higher complication rate than did moderately angulated (45 to 59°) stenoses, 6 of 48 (12.5%) versus 7 of 52 (13.5%), respectively. Furthermore, deliberate balloon undersizing to balloon:artery ratios of 0.80 to 0.90 did not appear to reduce the complication rate compared with normal sizing (balloon:artery ratios 0.91 to 1.00); 3 of 23 (13%) versus 3 of 45 (7%) (difference not significant), respectively.

DISCUSSION

Despite advances in angioplasty technique, major ischemic complications continue to occur in 3 to 5% of





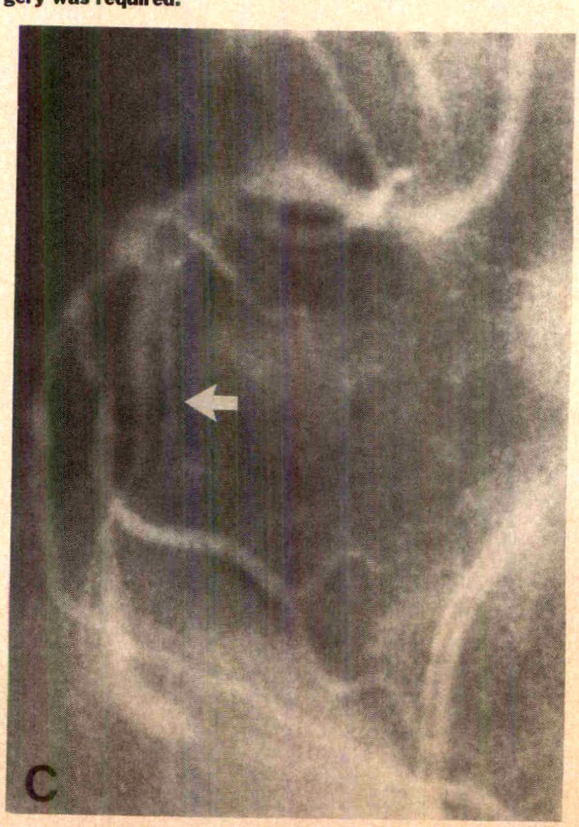


FIGURE 2. ***A,*** **left anterior oblique projection of a proximal 78%, 73° right coronary artery stenosis in an 85-year-old man with class IV angina pectoris.** ***B,*** **balloon inflation using a polyvinylchloride material balloon.** ***C,*** **the resultant propagated dissection** ***(arrow).*** **Emergency coronary artery bypass surgery was required.**

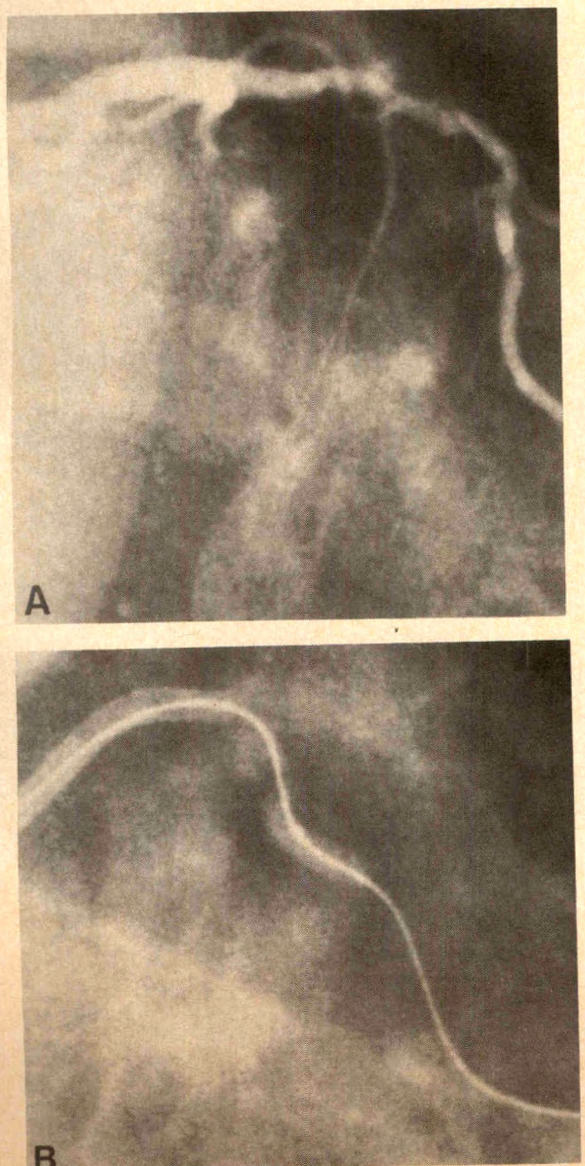
procedures.[9] Factors associated with a lessened likelihood of success and a heightened risk of complications, among them dilatation at a bend, are well recognized.[3,4,6] This study was undertaken to better understand which instances of bend dilatation pose the highest risk, and, if possible, to suggest ways to lessen that risk.

The results show that PTCA to sites with a ≥45° angulation was associated with only a 70% success rate and a 13% incidence of major ischemic complications, both considerably worse than the results with PTCA to nonangulated segments at this institution. The mechanism by which balloon inflation at a point of vessel angulation causes such a poor result appears to be due to arterial disruption from the balloon as it straightens, opens and tears the atherosclerotically fixed and rigid angulated arterial segment. Successful PTCA (Figure 3) was most closely correlated with use of polyethylene terephthalate balloons and absence of angiographically suggested thrombus (filling defect or staining), and major ischemic complications were significantly associated with advanced patient age, less experienced angioplasty operators, thrombus and longer lesions.

There have been no other comprehensive studies of the results of angioplasty for bend stenoses. Previous studies have consistently found PTCA risk to be associated with unstable angina pectoris,[9,10] advanced

TABLE I Clinical, Angiographic and Procedural Characteristics (n = 100)

Clinical characteristics	
Age (years)	60 ± 10
Current smoking (%)	58
Men (%)	70
Unstable angina pectoris (%)	42
Angiographic characteristics	
Active stenosis angle (%)	44
Bifurcation stenosis (%)	16
Calcium (%)	20
Chronic total occlusion (%)	2
Eccentricity (%)	56
Irregular contour (%)	21
Multivessel disease (%)	75
Ostial stenosis (%)	1
Percent diameter stenosis	69 ± 12
Stenosis angle (degrees)	62 ± 13
Stenosis length (mm)	5.2 ± 4.1
Thrombus (%)	7
Tortuosity (%)	7
Procedural characteristics	
Balloon: artery ratio	0.94 ± 0.13
Maximum inflation duration (sec)	103 ± 46
Maximum inflation pressure (atm)	8.0 ± 1.7
Number of inflations	3.8 ± 2.0
Predilatation to ≤5 atm (%)	51



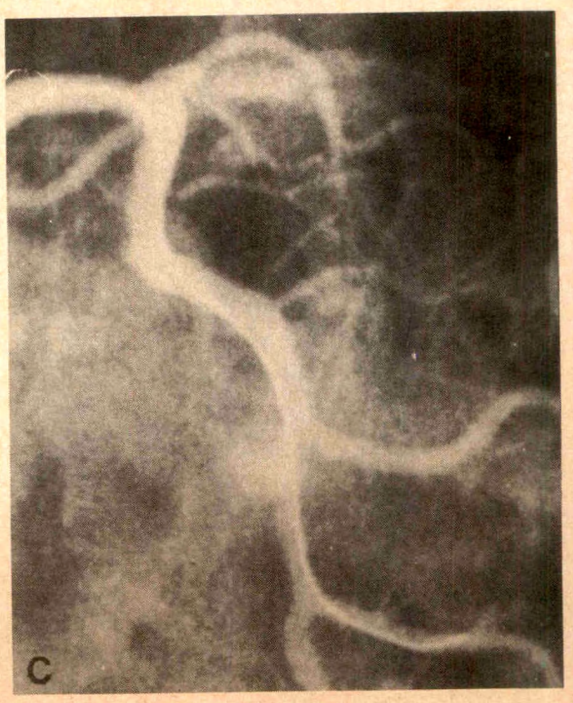


FIGURE 3. ***A*, caudally angulated right anterior oblique projection of a subtotally occluded, 77° (see *C*) left circumflex coronary artery stenosis in a 60-year-old man with class IV angina pectoris. *B*, balloon inflation using a polyethylene terephthalate material balloon. *C*, the resultant excellent angiographic result. There were no adverse clinical sequelae.**

TABLE II Correlates of Procedural Success

Characteristic	Success Group (n = 70)	Failure Group (n = 30)	Univariate p Value	Multivariate p Value
PET balloon material (%)	27.1	3.3	<0.001	0.003
Thrombus (%)	2.9	17.2	0.057	0.039
Stenosis length (mm)	4.6 ± 3.4	6.5 ± 5.3	0.081	0.101
Roughened contour (%)	14.5	36.7	0.028	0.104
Balloon: artery ratio <0.8 or ≥1.1 (%)	25.7	46.7	0.052	—
Age (yrs)	58 ± 8	62 ± 11	0.097	—
Number of ACC/AHA class B characteristics[6]	1.8 ± 1.4	2.2 ± 0.8	0.103	—

Values are mean ± standard deviation.
ACC = American College of Cardiology; AHA = American Heart Association; PET = polyethylene terephthalate.

TABLE III Correlates of Major Ischemic Complications*

Characteristics	Complication Group (n = 13)	No Complication Group (n = 87)	Univariate p Value	Multivariate p Value
Age (yrs)	66 ± 10	59 ± 9	0.011	0.034
Experienced PTCA operator (%)	61.5	80.5	0.19	0.048
Thrombus (%)	23.1	4.7	0.14	0.050
Stenosis length (mm)	7.7 ± 6.4	4.8 ± 3.6	0.11	0.052
Balloon: artery ratio <0.8 or ≥1.1 (%)	53.8	28.7	0.10	—
PET balloon material (%)	7.7	21.8	0.12	—

* Cardiac death, bypass surgery or myocardial infarction.
Values are mean ± standard deviation.
PET = polyethylene terephthalate; PTCA = percutaneous transluminal coronary angioplasty.

TABLE IV Relation of Balloon Dilatation Catheter Composition to Procedural Success

Catheter	Balloon Material	No.*	% Success
Sci Med Skinny™	PO	22/31	71.0
ACS Simpson Ultra Low Profile™	PE	10/14	71.4
USCI® LPS II	PVC	6/12	50.0
USCI® Profile Plus	PET	10/11	90.9
ACS Hartzler Micro™	PE	4/4	100.0
USCI® Mini	PET	4/4	100.0
USCI® LPS I	PVC	3/4	75.0
USCI® LPS II Short	PVC	3/3	100.0
USCI® Probe	PET	3/3	100.0
ACS Simpson-Robert™	PE	2/2	100.0
USCI® Simplus	PE	2/2	100.0
Sci Med Ace™	PO	1/2	50.0
ACS angled™	PE	0/1	0.0
ACS Simpson Ultra Low Profile II™	PE	0/1	0.0

* n = 94, due to failure secondary to inability to cross with balloon in 4 patients and wire-induced dissection in 2 patients.
PE = polyethylene; PET = polyethylene terephthalate; PO = polyolefin; PVC = polyvinylchloride.

age,[11,12] longer lesions,[4] thrombus,[4,13] diffuse disease[4] and balloon:artery ratios >1.1.[7] One report has suggested that experienced operators have better results with complex stenoses than less experienced operators.[14]

This study adds to current knowledge by emphasizing the particular importance of patient age, concomitant thrombus, lesion length and operator experience in this setting, and for the first time suggests that the balloon material may be related to the likelihood of success or to complications of angioplasty. In the absence of high-risk characteristics (age ≥65 years, thrombus or lesion length ≥10 mm), major ischemic events occurred at a rate only slightly greater than that associated with nonbend stenoses (4 of 56 = 7%; 95% confidence interval = 0 to 14%), whereas, in the presence of ≥1 of these high-risk features, major ischemic complications occurred at a prohibitively high rate (9 of 44 = 20.5%; 95% confidence interval = 14 to 26%). A long heparin infusion or the administration of thrombolytic agents may possibly be useful in decreasing the thrombus burden, which seems to be a covariable associated with adverse outcome.[15]

The importance of operator experience in minimizing the likelihood of major ischemic complications in high-risk patients has only been reported once previously in the voluminous body of angioplasty studies, yet it perhaps should not be surprising, given the known data on other surgical procedures.[16] Highly experienced operators had a 55% lower rate of major ischemic complications (10 vs 23%) in this series. This outcome could not be explained by differences between highly experienced and less experienced operators in the variables balloon:artery ratio, number of balloon inflations or number of class B ACC/AHA lesion characteristics of the stenosis dilated.

Angioplasty balloons that tend to conform to angulated arterial segments at high inflation pressures appear to improve procedural outcome in this setting. Bench studies in which an angioplasty balloon is inflated to 10 atm inside a standard acrylic model artery formed to a 90° angle have shown that polyethylene terephthalate material balloons deform (straighten) the model artery by 36 to 43°, whereas balloons made of

polyethylene or polyolefin cause deflections of 57 to 63° (McIntyre J, personal communication, 1989), possibly causing less straightening stress and propensity toward medial disruption (tearing). The low profile of polyethylene terephthalate balloons may also be useful in this setting. However, differing thicknesses of polyethylene terephthalate material balloons are currently under evaluation, and the results reported herein may not apply to all such balloons.

This study is limited by the relatively few number of cases studied and by the multiple statistical comparisons made. As such, one must not conclude that balloon composition alone defines the likelihood of procedural success for a given balloon and that high success rates cannot be achieved with equipment evaluated in small numbers in this study. Furthermore, subset analysis may be inconclusive (for example, the question as to whether polyethylene terephthalate balloons used in high-risk bend lesions would result in an acceptable complication rate is unanswered—with 1 of 9 (11%) [0 to 33%; 95% confidence intervals] having a major ischemic complication), and the likelihood of a statistical type II error is increased. In addition, subjectivity of assessment of arterial morphology must be recognized.[2,4] All evaluations in this study were performed by a single observer. Previous studies have reported, however, an interobserver variability of 12% for bend stenoses.[4]

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Quantitative Angiographic Comparison of the Immediate Success of Coronary Angioplasty, Coronary Atherectomy and Endoluminal Stenting

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Coronary atherectomy and coronary stenting effectively reduce the severity of coronary artery stenoses, but direct comparisons of these interventions with conventional balloon angioplasty have not been performed. To compare the immediate efficacy of these 3 interventions, the angiographic morphology and the severity of the residual coronary stenosis were quantitatively evaluated in 18 patients undergoing coronary atherectomy and in 21 patients treated by endoluminal coronary stenting. Each of these groups of patients was compared with a matched group of coronary angioplasty patients selected from a large, computerized database. The variables matched included patient age and sex, lesions site and severity, and lesion complexity. Both coronary atherectomy and coronary stenting more effectively reduced the severity of the coronary stenosis when compared with balloon angioplasty. The luminal diameter stenosis was reduced from 69 ± 10 to 22 ± 20% in the atherectomy group compared with a reduction from 74 ± 11 to 44 ± 14% in the matched coronary angioplasty population ($p = 0.008$). Similarly, the luminal diameter stenosis was reduced from 77 ± 11 to 26 ± 12% in the stented group compared with a reduction from 81 ± 10 to 42 ± 14% in the matched coronary angioplasty group ($p = 0.014$). In addition, moderate or severe coronary dissections were noted more frequently in the coronary angioplasty groups than in their respective atherectomy and stent groups (0 vs 33%, $p = 0.008$, and 5 vs 19%, $p = 0.15$, respectively). These data suggest that, in selected patients, both coronary atherectomy and coronary stenting more effectively reduce the severity of coronary stenoses when compared with conventional balloon angioplasty and that this may be achieved with a lower risk of medial dissection.

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Since its introduction by Gruentzig et al in 1979,[1] percutaneous transluminal coronary angioplasty (PTCA) has become a well-characterized technique for the relief of critical coronary artery stenoses. The procedure remains limited, however, by the risk of coronary dissection and abrupt closure of the dilated vessel in 3 to 5%,[2,3] and by recurrent stenosis at the site of dilatation.[4–8] Coronary atherectomy and endoluminal stenting are 2 alternative interventions that have the potential to overcome these limitations. Directional coronary atherectomy[9] physically removes obstructive atheromatous tissue, and endovascular stenting[10] maintains luminal diameter by compressing the arterial wall and preventing elastic recoil of the dilated arterial segment. By achieving a smoother, less disrupted arterial wall, these devices may reduce the stimulus for medical smooth muscle proliferation and coronary arterial restenosis. Therefore, to compare the immediate efficacy of these 2 procedures with that of conventional balloon angioplasty, the angiographic morphology and the severity of the residual, postprocedural stenosis were determined in a group of patients undergoing coronary atherectomy, in a group undergoing endoluminal stenting and in matched groups undergoing conventional balloon angioplasty.

METHODS

Between August 1988 and March 1989, 18 patients underwent coronary atherectomy with the Simpson directional coronary atherectomy device.[9] This over-the-wire device consists of a catheter-mounted, metallic capsule (Figure 1), and a central metallic blade that rotates at 2,500 revolutions/min. The open side of the capsule is held against the diseased arterial wall by low pressure inflation of a balloon mounted on the opposite side of the device. Atheromatous tissue is removed by the rotating blade, which is slowly advanced, pushing the excised tissue forward into a distal, conical collecting chamber. Each arterial quadrant is sequentially shaved. The device is then removed and atheromatous fragments are retrieved from the distal chamber. During the study period, patients were considered eligible for atherectomy if they had a coronary stenosis in a relatively straight segment of 1 of the 3 major epicardial vessels, without proximal tortuosity or heavy calcification. Each patient received oral aspirin ≥24 hours before the procedure. Intravenous heparin (15,000 IU) was given after the initial guiding angiograms and further doses of 5,000 IU were given each hour to maintain anticoagulation during the procedure.

TABLE I Angiographic and Demographic Characteristics of Atherectomy and Stent Groups and of their Respective Matched Angioplasty Groups

	Atherectomy (n = 18)	PTCA-Atherectomy (n = 18)	Stent (n = 21)	PTCA-Stent (n = 21)
Age (yrs)*	57 ± 12	56 ± 12	58 ± 10	56 ± 10
Sex (M/F)	16/2	16/2	16/5	16/5
Prior PTCA	10	4	12	4
Stenosis site (proximal/mid/distal)				
Left anterior descending	10/6/0	8/8/0	3/5/0	3/5/0
Right	0/0/2	0/0/2	3/7/0	2/7/1
Circumflex	0/0/0	0/0/0	1/1/1	2/0/1
Initial TIMI grade flow				
3	12	8	10	8
2	6	9	6	9
1	0	1	4	3
0	0	0	1	1
Initial morphology (ACC/AHA Classification)				
Type A	10	8	10	12
Type B	8	10	11	8
Type C	0	0	1	1
Absolute diameter (mm)*				
Initial	1.0 ± 0.5	0.7 ± 0.3	0.7 ± 0.3	0.6 ± 0.3
Final	2.5 ± 0.6	1.6 ± 0.5	2.4 ± 0.4	1.7 ± 0.4
Change	1.5 ± 0.6	0.9 ± 0.5	1.6 ± 0.5	1.2 ± 0.5

* Mean ± standard deviation.
ACC = American College of Cardiology; AHA = American Heart Association; F = female; M = male; PTCA = percutaneous transluminal coronary angioplasty; PTCA-Atherectomy = coronary angioplasty group matched with the atherectomy group; PTCA-Stent = coronary angioplasty group matched with the stented group; TIMI = Thrombolysis in Myocardial Infarction.

Over the same period, Palmaz-Schatz coronary stents[10] were inserted into the stenosed coronary arterial segments of 21 patients. Indications for coronary stenting were similar to those for coronary atherectomy. After balloon dilatation of the diseased segment, the cylindrical, stainless steel wire mesh stents (Figure 2) were delivered on a conventional coronary angioplasty balloon that was inflated to expand the stent to the required size. The design of the stent ensures that, once dilated, the device retains its expanded form, preventing elastic recoil of the arterial wall. Each patient received oral aspirin and dipyridamole, intravenous dextran and 15,000 IU intravenous heparin before the insertion of the stent, and intravenous heparin was continued for a period of ≥24 hours after the procedure. Neither intravenous nor intracoronary nitroglycerin was given routinely during coronary atherectomy or coronary stenting.

The postprocedural angiographic characteristics of the 18 atherectomy and 21 stented patients were compared with those of matched populations (PTCA-atherectomy and PTCA-stent, respectively) selected from a large, elective coronary angioplasty database. The computer-matched variables included patient age and sex, and the site and severity of the coronary stenosis. Consideration was also given to whether the stenosis was a new lesion or a recurrent stenosis following a previous coronary intervention. However, relatively few procedures in the angioplasty database were performed on recurrent stenoses, thus limiting the possibility of a close match for this variable. After identification of several potential patient matches, an attempt was also made, by comparison of the baseline angiograms, to match for lesion complexity based on the lesion length, angulation and degree of proximal tortuosity. Patients from the database were not considered for matching if coronary angioplasty failed to reduce the target stenosis to <50% luminal diameter stenosis by visual estimate. No attempt was made to match the atherectomy group with the stent group or to compare their respective outcomes directly.

Analysis of the immediate angiographic result of each procedure was performed using an automated, computerized edge-detection algorithm (Artrek) that

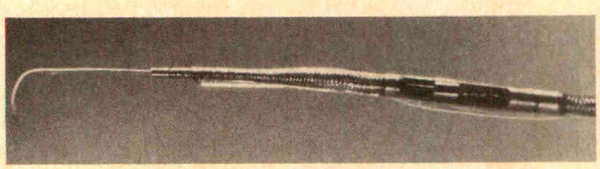


FIGURE 1. The Simpson directional coronary atherectomy device.

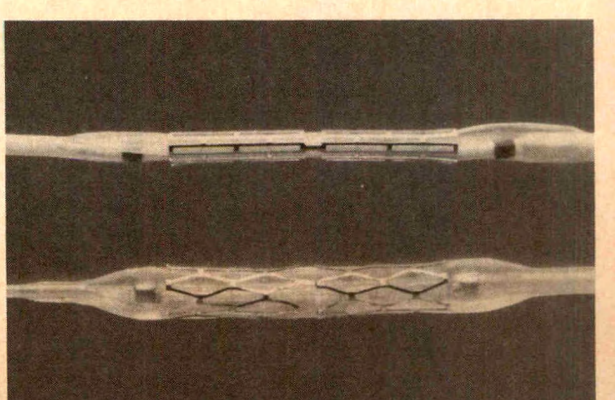


FIGURE 2. The Palmaz-Schatz coronary stent before and after balloon inflation.

has been previously described and validated.[11] Preprocedural coronary stenosis severity was quantitated in the single tightest angiographic projection by a single observer unaware of which procedure was subsequently performed. Postprocedural analysis was performed in the identical projection as the initial measurement by the same observer blinded, to the extent possible, from treatment modality. Coronary arterial morphology at the site of intervention was also recorded. Acute coronary dissection was graded as being absent, mild (if a minor disruption occurred in the endothelial contour), moderate (if a linear extraluminal opacity or intraluminal filling defect was apparent) or severe (if a spiral dissection extended beyond the length of the dilated lesion or resulted in compromised coronary flow).

Statistics: All data are expressed as mean ± 1 standard deviation. Comparison of the severity of the residual stenosis between the groups was performed using the unpaired Student *t* test and differences were considered to be statistically significant at $p < 0.05$. The incidence of acute dissection was compared using the chi-square test.

RESULTS

Baseline demographic and angiographic characteristics of the atherectomy group, the stent group and of the 2 respective matched angioplasty groups are listed in Table I. The groups were well matched for age, sex, lesion site and initial lesion morphology. However, a noticeably higher proportion of the lesions treated with the newer devices were recurrent stenoses following prior coronary angioplasties. Of the 18 atherectomy patients, 10 had had a prior angioplasty compared with 4 of the matched angioplasty group. Similarly, 12 of the 21 stent patients had had prior angioplasty compared with 4 of the matched group. This reflects early referral patterns and selection criteria for stent implantation and atherectomy.

Before the interventional procedure, the severity of the coronary stenosis was similar in each of the groups (Figures 3 and 4). Lesion morphology (American College of Cardiology/American Heart Association classification) was also similar in the matched groups, but a slightly higher proportion of each angioplasty group had coronary flow less than Thrombolysis in Myocardial Infarction grade 3 (Table I). Both atherectomy and coronary stenting resulted in significantly greater improvements in coronary luminal diameter than was achieved in their respective matched angioplasty populations. The postatherectomy luminal diameter stenosis was reduced to 22 ± 20% compared with 44 ± 14% in the angioplasty group ($p = 0.0006$) (Figure 3), and the absolute diameter was increased by 1.5 ± 0.6 mm compared with 0.9 ± 0.5 mm ($p < 0.003$) (Table I). Similarly, the final luminal diameter stenosis in the stented patients was 26 ± 12% compared with 42 ± 14% in the corresponding angioplasty group ($p = 0.0003$) and the absolute diameter was increased by 1.6 ± 0.5 mm compared with 1.2 ± 0.5 mm ($p < 0.009$). Importantly, there did not appear to be any evidence of procedure-related coronary vasoconstriction. Although intracoronary nitroglycerin was not given routinely, there were no significant changes in the caliber of the proximal reference segment of the treated coronary artery in the atherectomy group (3.1 ± 0.6 vs 3.2 ± 0.5 mm), the stented group (3.2 ± 0.5 vs 3.4 ± 0.9 mm) or in the PTCA-atherectomy and PTCA-stent groups (2.8 ± 0.6 vs 2.8 ± 0.5 mm, and 3.0 ± 0.5 vs 3.0 ± 0.5 mm, respectively). The incidence of moderate or severe dissection was, however, significantly higher after balloon angioplasty than after atherectomy (0 vs 33%; $p = 0.008$) (Figure 5). Dissections of at least moderate severity were also less frequent after the stent procedures than in

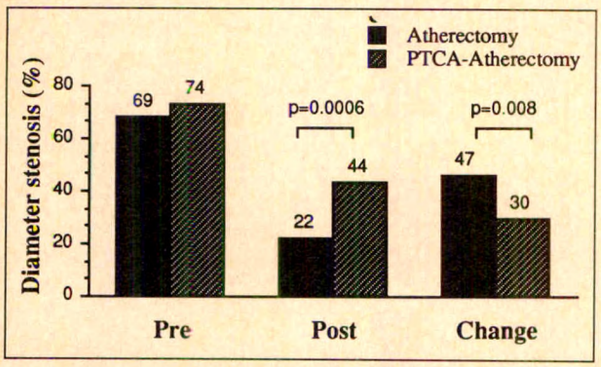


FIGURE 3. Comparison of the coronary luminal diameter stenosis before and after intervention in the atherectomy group and its matched angioplasty group (PTCA-Atherectomy).

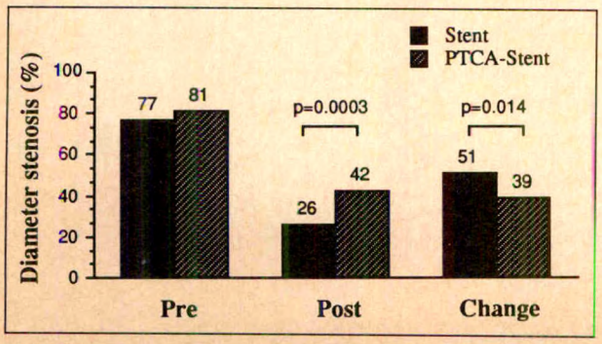


FIGURE 4. Comparison of the coronary luminal diameter stenosis before and after intervention in the stented group and in the matched angioplasty group (PTCA-Stent).

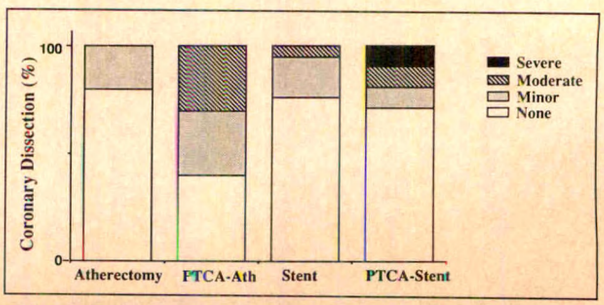


FIGURE 5. Incidence and severity of postprocedural coronary dissection in the atherectomy and stented groups and in their respective matched angioplasty groups. Ath = atherectomy; other abbreviations as in Figures 3 and 4.

the corresponding PTCA group, but the difference did not reach statistical significance (5 vs 19%, p = 0.15).

DISCUSSION

Immediate angiographic results: The principal finding of this study was that both directional coronary atherectomy and endovascular stenting achieved a greater reduction in the severity of obstructive coronary stenoses than was achieved in matched populations using conventional balloon angioplasty. In addition, use of these devices was associated with a lower incidence of coronary arterial dissection. Although the study was not designed to compare coronary atherectomy directly with stenting, there did not appear to be any substantial difference in the angiographic results of the 2 interventions.

The relatively high residual stenosis and high incidence of dissection after coronary angioplasty in this study are consistent with the known mechanisms by which balloon angioplasty improves coronary luminal dimensions and with the associated pathologic changes observed early after the procedure. These mechanisms include stretching of the arterial wall, endothelial disruption, plaque fracture and medial dissection.[12–14] Similar pathologic changes undoubtedly occur during the insertion of coronary stents, but the disrupted layers of the arterial wall are splinted by the meshwork of the device. This may allow the safe use of larger angioplasty balloons and higher inflation pressures during stent implantation, a factor that may have contributed to the better immediate results noted in this study. Coronary atherectomy, on the other hand, appears to depend less on stretching of the vascular wall and more on the excision of atheromatous material. During the immediate post-angioplasty period, some of the initial increase in luminal diameter and cross-sectional area may be diminished by passive, elastic recoil of the arterial wall or by coronary vasoconstriction,[15] mediated by endothelially derived vasoconstrictive factors.[16] Both of these factors are effectively minimized by endovascular stenting. Whether coronary atherectomy also reduces the propensity for elastic recoil and coronary vasoconstriction by removing or injuring medial smooth muscle has not been evaluated.

Vascular disruption: The greater improvement in coronary luminal dimensions after coronary stenting and coronary atherectomy was associated with a lower incidence of coronary dissection than was apparent after conventional balloon angioplasty. This suggests that these interventions may reduce the likelihood of acute closure of the vessel and therefore increase the safety of the procedure. Coronary stents have, in fact, been used successfully both to treat and to prevent acute closure after balloon angioplasty-induced intimal dissection.[17]

Immediate angiographic results and restenosis: Whether the apparently superior immediate results achieved with these new devices will be associated with a reduction in the incidence of recurrent stenosis is not yet clear. The factors that trigger medial smooth muscle cell migration and proliferation remain poorly understood. The incidence of restenosis after balloon angioplasty has been correlated with the severity of the residual coronary stenosis and the presence of a residual translesional gradient.[4,18] Deep arterial injury that exposes a large surface area of collagen may also increase the stimulus for smooth muscle cell proliferation.[19] Conceivably, endovascular stents may reduce the likelihood of restenosis by "sealing" intimal flaps and minimizing the amount of exposed collagen. Furthermore, the greater caliber achieved after stent implantation may minimize the functional importance of subsequent intimal proliferation.[20] Conversely, atherectomy greatly increases the exposure of medial (and occasionally adventitial) collagen and may actually increase the likelihood of restenosis. At this point, the pathophysiology of restenosis after the newer interventions remains conjectural. Preliminary data suggest, however, that neither device will eliminate this problem.[20,21]

Study limitations: The major limitation of this study is that it is a retrospective, nonrandomized study. Although the 2 groups are well matched for several demographic and angiographic variables, differences between them may be important. For example, a greater proportion of the lesions treated by stenting or atherectomy were recurrent stenoses following previous balloon dilatation. The inherently different underlying pathologic substrates between new and recurrent stenoses may have influenced the ease of the procedure and the likelihood of acute complications,[3] a factor that, in this study, would favor the atherectomy and stent groups. Second, this study was a comparison of *successful* coronary interventions and may not be fully representative of the total population on whom percutaneous interventions are attempted. Finally, because of the relatively small number of patients treated with the newer devices, it was not possible to match the stent population with the population undergoing coronary atherectomy. For this reason, no direct comparison can be made between these 2 procedures. These considerations suggest that a randomized, controlled clinical trial is warranted to compare the immediate angiographic results and the long-term efficacy of each of these 3 interventions.

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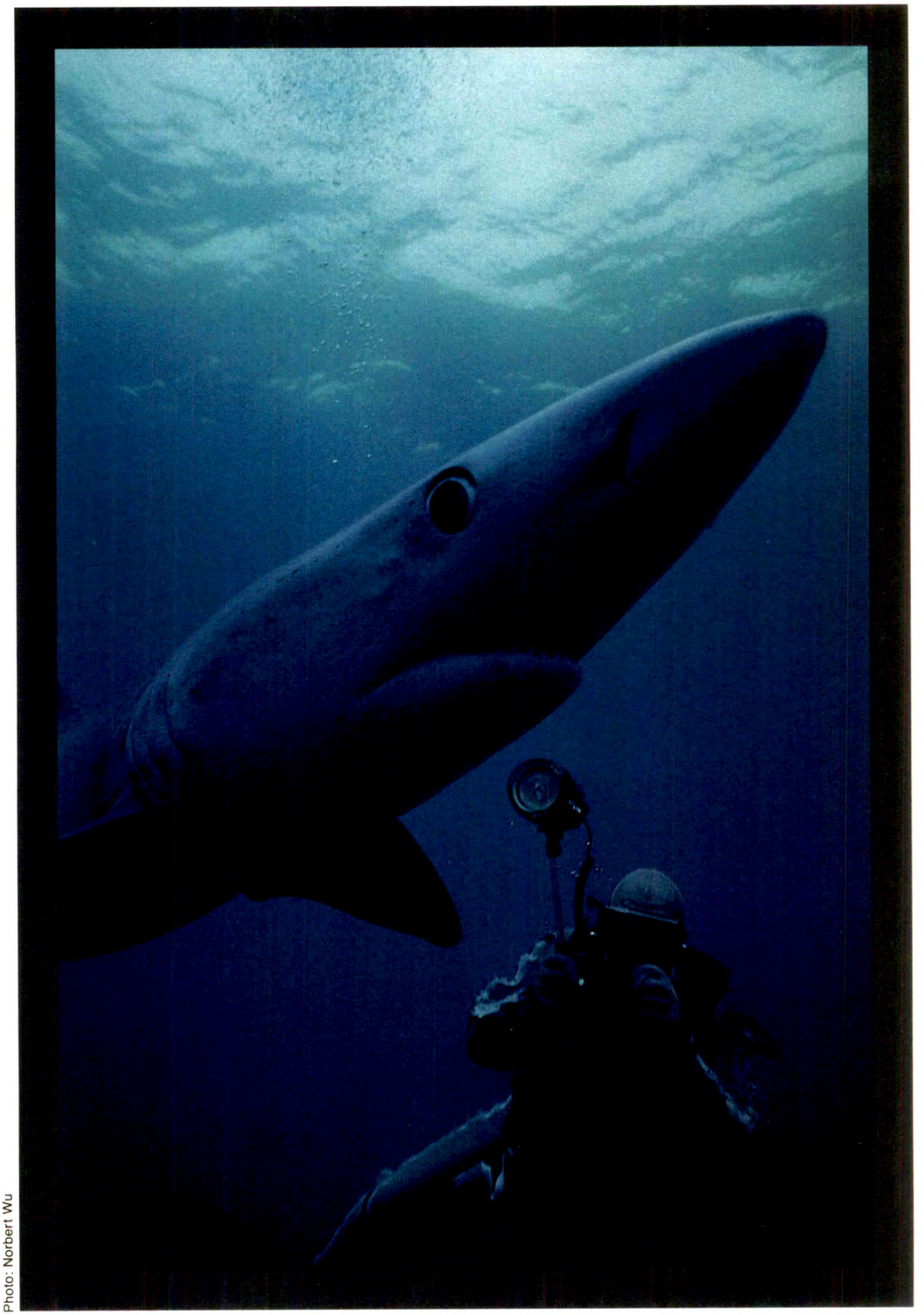


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All in all, OPTIRAY® is quite a contrast. Please contact your Mallinckrodt Cardiology representative for more information, or call us toll free at (800) 325-3688.

All nonionic iodinated contrast media currently available inhibit blood coagulation, in vitro, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary to minimize thromboembolic events.

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OPTIRAY® 160 240 320
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DESCRIPTION: Each milliliter of OPTIRAY 160 (ioversol injection 34%) provides 339 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 160 provides 16% (160 mg/mL) organically bound iodine.

Each milliliter of OPTIRAY 240 (ioversol injection 51%) provides 509 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 240 provides 24% (240 mg/mL) organically bound iodine.

Each milliliter of OPTIRAY 320 (ioversol injection 68%) provides 678 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 320 provides 32% (320 mg/mL) organically bound iodine.

CONTRAINDICATIONS: None.

WARNINGS: Nonionic iodinated contrast media inhibit blood coagulation, in vitro, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, catheter and syringe material, underlying disease state and concomitant medications may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended including close attention to guidewire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing with heparinized saline solutions and minimizing the length of the procedure. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of in vitro clotting.

Serious or fatal reactions have been associated with the administration of iodine-containing radiopaque media. It is of utmost importance to be completely prepared to treat any contrast medium reaction.

As with any contrast medium, serious neurologic sequelae, including permanent paralysis, can occur following cerebral arteriography, selective spinal arteriography and arteriography of vessels supplying the spinal cord. A cause-effect relationship to the contrast medium has not been established since the patients' pre-existing condition and procedural technique are causative factors in themselves. The arterial injection of a contrast medium should never be made following the administration of vasopressors since they strongly potentiate neurologic effects.

Caution must be exercised in patients with severely impaired renal function, combined renal and hepatic disease, severe thyrotoxicosis, myelomatosis, or anuria, particularly when large doses are administered.

Intravascularly administered iodine-containing radiopaque media are potentially hazardous in patients with multiple myeloma or other paraproteinemia, particularly in those with therapeutically resistant anuria. Myeloma occurs most commonly in persons over age 40. Although neither the contrast agent nor dehydration has been proved separately to be the cause of anuria in myelomatous patients, it has been speculated that the combination of both may be causative. The risk in myelomatous patients is not a contraindication to the procedure; however, special precautions, including maintenance of normal hydration and close monitoring, are required. Partial dehydration in the preparation of these patients prior to injection is not recommended since this may predispose the patient to precipitation of the myeloma protein.

Administration of radiopaque materials to patients known or suspected of having pheochromocytoma should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the procedures may be performed; however, the amount of radiopaque medium injected should be kept to an absolute minimum. The blood pressure should be assessed throughout the procedure, and measures for treatment of a hypertensive crisis should be available.

Contrast media may promote sickling in individuals who are homozygous for sickle cell disease when administered intravascularly.

Reports of thyroid storm following the intravascular use of iodinated radiopaque agents in patients with hyperthyroidism or with an autonomously functioning thyroid nodule, suggest that this additional risk be evaluated in such patients before use of any contrast medium.

PRECAUTIONS: *General:* Diagnostic procedures which involve the use of iodinated intravascular contrast agents should be carried out under the direction of personnel skilled and experienced in the particular procedure to be performed. A fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognizing and treating adverse reactions of all types should always be available. Since severe delayed reactions have been known to occur, emergency facilities and competent personnel should be available for at least 30 to 60 minutes after administration.

Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, diabetic patients, and in susceptible non-diabetic patients (often elderly with pre-existing renal disease). *Patients should be well hydrated prior to and following the administration of OPTIRAY.*

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions, should always be considered (See ADVERSE REACTIONS). Increased risk is associated with a history of previous reaction to a contrast medium, a known sensitivity to iodine and known allergies (i.e., bronchial asthma, hay fever and food allergies) or hypersensitivities.

The occurrence of severe idiosyncratic reactions has prompted the use of several pretesting methods. However, pretesting cannot be relied upon to predict severe reactions and may itself be hazardous to the patient. It is suggested that a thorough medical history with emphasis on allergy and hypersensitivity, prior to the injection of any contrast medium, may be more accurate than pretesting in predicting potential adverse reactions. A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent when a diagnostic procedure is thought essential, but caution should be exercised. Premedication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions in such patients should be considered. Reports indicate that such pretreatment does not prevent serious life-threatening reactions, but may reduce both their incidence and severity.

General anesthesia may be indicated in the performance of some procedures in selected patients; however, a higher incidence of adverse reactions has been reported in these patients, and may be attributable to the inability of the patient to identify untoward symptoms or to the hypotensive effect of anesthesia which can prolong the circulation time and increase the duration of exposure to the contrast agent.

In angiographic procedures, the possibility of dislodging plaques or damaging or perforating the vessel wall should be considered during catheter manipulations and contrast medium injection. Test injections to insure proper catheter placement are suggested.

Angiography should be avoided whenever possible in patients with homocystinuria because of the risk of inducing thrombosis and embolism.

Patients with congestive heart failure should be observed for several hours following the procedure to detect delayed hemodynamic disturbances which may be associated with a transitory increase in the circulating osmotic load.

Selective coronary arteriography should be performed only in selected patients and those in whom the expected benefits outweigh the procedural risk. The inherent risks of angiocardiography in patients with chronic pulmonary emphysema must be weighed against the necessity for performing this procedure.

Extreme caution during injection of a contrast medium is necessary to avoid extravasation. This is especially important in patients with severe arterial or venous disease.

Drug Interactions: Renal toxicity has been reported in a few patients with liver dysfunction who were given oral cholecystographic agents followed by intravascular contrast agents. Administration of any intravascular contrast agent should therefore be postponed in patients who have recently received a cholecystographic contrast agent.

Other drugs should not be mixed with ioversol injection.

Drug Laboratory Test Interactions: The results of PBI and radioactive iodine uptake studies, which depend on iodine estimation, will not accurately reflect thyroid function for up to 16 days following administration of iodinated contrast media. However, thyroid function tests not depending on iodine estimations, e.g., T3 resin uptake and total or free thyroxine (T4) assays are not affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long term animal studies have been performed to evaluate carcinogenic potential. However, animal studies suggest that this drug is not mutagenic and does not affect fertility.

Pregnancy Category B: No teratogenic effects attributable to ioversol have been observed in teratology studies performed in animals. There are, however, no adequate and well controlled studies in pregnant women. It is not known whether ioversol crosses the placental barrier or reaches fetal tissues. However, many injectable contrast agents cross the placental barrier in humans and appear to enter fetal tissue passively. Because animal teratology studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. X-ray procedures involve a certain risk related to the exposure of the fetus.

Nursing Mothers: It is not known whether ioversol is excreted in human milk. However, many injectable contrast agents are excreted unchanged in human milk. Although it has not been established that serious adverse reactions occur in nursing infants, caution should be exercised when intravascular contrast media are administered to nursing women because of potential adverse reactions, and consideration should be given to temporarily discontinuing nursing.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Adverse reactions following the use of OPTIRAY formulations are usually mild to moderate, of short duration and resolve spontaneously (without treatment). However, serious, life-threatening and fatal reactions, mostly of cardiovascular origin, have been associated with the administration of iodine-containing contrast media.

Injections of contrast media are often associated with sensations of warmth and pain. In controlled double-blind clinical studies, significantly less warmth and pain were associated with the injection of OPTIRAY than with iothalamate meglumine, diatrizoate meglumine, and diatrizoate meglumine and diatrizoate sodium.

When OPTIRAY 320 is used for coronary arteriography and ventriculography in double-blind clinical trials, electrocardiographic and hemodynamic changes occur with less frequency and severity with ioversol injection than with diatrizoate meglumine and diatrizoate sodium.

Following coronary artery and left ventricular injection, electrocardiographic parameters were affected less with OPTIRAY (ioversol injection) than with diatrizoate meglumine and diatrizoate sodium injection. These parameters included the following: bradycardia, tachycardia, T-wave amplitude, ST depression and ST elevation.

OPTIRAY has also been shown to cause fewer changes in cardiac function and systemic blood pressure than conventional ionic media. These include cardiac output, left ventricular systolic and end-diastolic pressure, right ventricular systolic and pulmonary artery systolic pressures and decreases in systolic and diastolic blood pressures.

The following table of incidence of reactions is based upon clinical trials with OPTIRAY formulations in over 1100 patients. This listing includes all adverse reactions which were coincidental to the administration of ioversol regardless of their direct attributability to the drug or the procedure. Adverse reactions are listed by organ system and in decreasing order of occurrence. Significantly more severe reactions are listed before others in a system regardless of frequency.

Adverse Reactions

System	> 1%	≤ 1%
Cardiovascular	none	angina pectoris hypotension vascular spasm bradycardia conduction defect false aneurysm hypertension transient arrhythmia vascular trauma
Digestive	none	nausea vomiting
Nervous	none	cerebral infarct headache blurred vision vertigo lightheadedness vasovagal reaction disorientation dysphasia paresthesia visual hallucination
Respiratory	none	laryngeal edema nasal congestion sneezing coughing hypoxia
Skin	none	periorbital edema urticaria facial edema flush pruritus
Miscellaneous	none	extravasation shaking chills bad taste general pain

Regardless of the contrast medium employed, the overall incidence of serious adverse reaction is higher with coronary arteriography than with other procedures. Cardiac decompensation, serious arrhythmias, myocardial ischemia or myocardial infarction may occur during coronary arteriography and left ventriculography.

General Adverse Reactions to Contrast Media

The following adverse reactions are possible with any parenterally administered iodinated contrast medium. Severe life-threatening reactions and fatalities, mostly of cardiovascular origin, have occurred. Most deaths occur during injection or 5 to 10 minutes later; the main feature being cardiac arrest with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. Based upon clinical literature, reported deaths from the administration of conventional iodinated contrast agents range from 6.6 per 1 million (0.00066 percent) to 1 in 10,000 patients (0.01 percent).

The reported incidence of adverse reactions to contrast media in patients with a history of allergy is twice that of the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations.

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions.

Chemotoxic reactions result from the physicochemical properties of the contrast medium, the dose and the speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the dose injected, the speed of injection, the mode of injection and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

In addition to the adverse reactions reported for ioversol, the following additional adverse reactions have been reported with the use of other contrast agents and are possible with any water soluble, iodinated contrast agent.

Nervous: muscular spasm, convulsions, aphasia, syncope, paralysis, visual field losses which are usually transient but may be permanent, coma and death.

Cardiovascular: angioneurotic edema, peripheral edema, vasodilation, thrombosis and rarely thrombophlebitis, disseminated intravascular coagulation and shock.

Skin: maculopapular rash, erythema, conjunctival symptoms, ecchymosis and tissue necrosis.

Respiratory: choking, dyspnea, wheezing which may be an initial manifestation of more severe and infrequent reactions including asthmatic attack, laryngospasm and bronchospasm, pulmonary edema, apnea and cyanosis. Rarely these allergic-type reactions can progress into anaphylaxis with loss of consciousness, coma, severe cardiovascular disturbances and death.

Miscellaneous: hyperthermia, temporary anuria or other nephropathy.

Other reactions may also occur with the use of any contrast agent as a consequence of the procedural hazard; these include hemorrhage or pseudoaneurysms at the puncture site, brachial plexus palsy following axillary artery injections, chest pain, myocardial infarction, and transient changes in hepatorenal chemistry tests. Arterial thrombosis, displacement of arterial plaques, venous thrombosis, dissection of the coronary vessels and transient sinus arrest are rare complications.

In cerebral arteriography, cardiovascular reactions that may occur with some frequency are bradycardia and either an increase or decrease in systemic blood pressure. Neurological reactions that may occur are: seizures, drowsiness, transient paresis, and mild disturbances in vision.

Central nervous system reactions with OPTIRAY in controlled clinical studies in cerebral arteriography that occurred with frequencies greater than 1% were: vertigo (4%) and blurred vision (3%).

In aortography, depending on the technique employed, the risks of this procedure also include the following: injury to the aorta and neighboring organs, pleural puncture, renal damage including infarction and acute tubular necrosis with oliguria and anuria, retroperitoneal hemorrhage from the translumbar approach and spinal cord injury and pathology associated with the syndrome of transverse myelitis. Under conditions of slowed aortic circulation there is an increased likelihood for aortography to cause muscle spasm. Occasional serious neurologic complications, including paraplegia, have also been reported in patients with aortoiliac obstruction, femoral artery obstruction, abdominal compression, hypotension, hypertension, spinal anesthesia, and injection of vasopressors to increase contrast. In these patients the concentration, volume, and number of repeat injections of the medium should be maintained at a minimum with appropriate intervals between injections. The position of the patient and catheter tip should be carefully monitored.

Entry of a large aortic dose into the renal artery may cause, even in the absence of symptoms, albuminuria, hematuria, and an elevated creatinine and urea nitrogen. Rapid and complete return of function usually follows.

Cardiovascular system reactions with OPTIRAY in controlled clinical studies in coronary arteriography with left ventriculography that occurred with frequencies greater than 1% were: angina (1.2%) and nausea (1.2%).

PRECAUTIONS FOR SPECIFIC PROCEDURES:

Cerebral Arteriography

Extreme caution is advised in patients with advanced arteriosclerosis, severe hypertension, cardiac decompensation, senility, recent cerebral thrombosis or embolism, and migraine.

Peripheral Arteriography

Pulsation should be present in the artery to be injected. In thromboangiitis obliterans, or ascending infection associated with severe ischemia, angiography should be performed with extreme caution, if at all.

Coronary Arteriography and Left Ventriculography

Mandatory prerequisites to the procedure are specialized personnel, ECG monitoring apparatus and adequate facilities for immediate resuscitation and cardioversion. Electrocardiograms and vital signs should be routinely monitored throughout the procedure.

Venography

Special care is required when venography is performed in patients with suspected thrombosis, phlebitis, severe ischemic disease, local infection or a totally obstructed venous system. In order to minimize extravasation during injection, fluoroscopy is recommended.

OVERDOSAGE: The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular system. Treatment of an overdosage is directed toward the support of all vital functions, and prompt institution of symptomatic therapy.

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Early Postoperative Balloon Coronary Angioplasty for Failed Coronary Artery Bypass Grafting

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In a small number of patients, coronary artery bypass grafting (CABG) fails to relieve anginal symptoms. The usefulness of coronary angioplasty for the treatment of early (≤90 days) recurrent ischemia after CABG was examined. Forty-five patients were treated from 2 to 90 days after CABG, including 8 patients studied emergently for prolonged ischemic symptoms. One-, 2- and 3-vessel native disease was found in 4, 10 and 31 patients, respectively. At the time of postoperative angiography, the major anatomic mechanism of recurrent ischemia was complete vein graft occlusion in 12 patients (27%), internal mammary artery occlusion in 3 (7%), vein graft stenoses in 13 (29%), internal mammary artery stenoses in 10 (22%), unbypassed disease in 4 (8%) and disease distal to the graft insertion site in 3 (7%). Angioplasty was successful at 91 of 98 sites (93%), including 95% of 41 lesions in native arteries, 89% of 46 lesions in vein grafts and 100% of 11 internal mammary artery lesions attempted. Complete revascularization was achieved in 84% of patients. There were 2 in-hospital deaths and 2 myocardial infarctions. Two additional patients underwent repeat CABG before discharge after uncomplicated but unsuccessful angioplasty. At late follow-up of the 43 survivors (mean 44 months), there were 4 deaths, 2 of which were noncardiac. Repeat CABG was required in only 3 patients and repeat angioplasty was performed in 10. Angina was absent or minimal in 35 patients; 17 patients were employed full time. Thus, percutaneous transluminal coronary angioplasty can relieve myocardial ischemia after unsuccessful CABG in the majority of patients.

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Coronary artery bypass grafting (CABG) performed for the control of angina pectoris leads to early postoperative relief from symptoms in most patients.[1–3] Late follow-up of patients treated with CABG reveals the return of angina pectoris in a growing proportion of patients over time.[3,4] Although percutaneous transluminal coronary angioplasty has been used to manage recurrent ischemia in patients late after CABG,[5–16] the role of coronary angioplasty in patients with recurrent myocardial ischemia early after CABG has not been adequately described. The purpose of this report was to characterize clinical and angiographic profiles of patients requiring coronary angioplasty ≤90 days of CABG and to report the usefulness of this treatment for relieving subsequent ischemia.

METHODS

Patient selection: Of 9,401 coronary angioplasty procedures performed between 1980 and 1989, 2,070 were in patients with ≥1 prior CABG operations (22%). All patients with coronary angioplasty ≤90 days of CABG were retrospectively identified. Forty-five patients met these selection criteria. Twenty-six patients were operated on at this institution, representing <1% of all patients referred for surgery during the study period. Clinical profiles, procedural records and long-term outcome were available for all patients.

Angioplasty protocol: After placement of the femoral sheath, patients received 10,000 IU heparin intravenously. Unless contraindicated, routine premedications consisted of 325 mg aspirin orally, 5 mg isosorbide dinitrate sublingually, 75 mg lidocaine intravenously and 5 mg verapamil intravenously. An additional 5,000 IU of heparin were given hourly during the procedure. In general, dilatation of all stenoses was attempted. Coronary angioplasty was performed with standard balloon catheters. Intracoronary thrombolytic therapy was used at the discretion of the primary dilator and was not dictated by protocol. After angioplasty, heparin therapy was continued for 18 to 24 hours and the partial thromboplastin time was maintained at 2 to 4 times the control level.

Definitions: A significant stenosis was defined as a reduction in luminal diameter of ≥70% compared with an adjacent segment in >1 projection. Angiographic success was defined as a postangioplasty luminal narrowing ≤40%. Complete procedural success was defined as successful dilatation of all stenoses attempted without

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TABLE I Major Anatomic Mechanisms for Early Postoperative Myocardial Ischemia in 45 Patients

	Pt. (%)
Vein graft occlusion	12 (27)
Internal mammary artery occlusion	3 (7)
Distal vein graft stenosis	13 (29)
Distal internal mammary artery stenosis	10 (22)
Unbypassed arteries	4 (8)
Narrowing distal to graft insertion	3 (7)

TABLE II Results of Angioplasty in 45 Patients Treated Early After Coronary Artery Bypass Grafting

	No.	(%)
Location of stenosis attempted		
Right coronary artery	12	
LAD	11	
LC	14	
Left main coronary artery	4	
Saphenous vein graft (right)	20	
Saphenous vein graft (LAD)	15	
Saphenous vein graft (LC)	11	
Internal mammary artery	11	
Results of angioplasty (success/attempts)		
Native arteries	39/41	(95)
Vein grafts	41/46	(89)
Internal mammary artery grafts	11/11	(100)
No. of pts		
Multilesion angioplasty	27/45	(60)
Multivessel angioplasty	21/45	(45)

LAD = left anterior descending; LC = left circumflex.

major complications (death, myocardial infarction or in-hospital CABG). Myocardial infarction was defined as a creatine kinase level more than twice normal with an elevated MB isoenzyme fraction. Measurements were obtained if angina or electrocardiographic changes occurred after the procedure. Impaired left ventricular function was defined as a left ventricular ejection fraction ≤40%. Complete revascularization was considered to be achieved when all significant stenoses were either bypassed by a patent graft or reduced to ≤40% after coronary angioplasty.

Follow-up: One aspirin daily was continued indefinitely and a calcium antagonist was generally prescribed for 2 to 3 months after discharge. Follow-up information was obtained through telephone interviews with the patient or surviving relatives.

RESULTS

Clinical characteristics: Prior CABG had been performed once in 40 patients and twice previously in 5 patients. The mean time between the most recent CABG and the early postoperative coronary angioplasty was 49 days (range 2 to 90). There were 38 men and 7 women, aged 38 to 77 years (mean 59). Seven patients (16%) were ≥70 years old. Postoperative cardiac catheterization was prompted by angina pectoris in 43 patients and by positive results in exercise tests performed for atypical symptoms in 2 patients. According to the New York Heart Association (NYHA) classification of angina, 27 patients were functional class IV, 10 were class III and 6 were class II. In 37 patients, catheterization was performed electively, whereas in 8 patients it was performed emergently for prolonged ischemic symptoms without ST-segment elevation indicating myocardial infarction. Diabetes mellitus requiring therapy was present in 3 patients.

Angiographic characteristics: One-, 2- and 3-vessel native coronary artery disease was present in 4, 10 and 31 patients, respectively. The mean resting left ventricular ejection fraction, available in 36 patients, was 58% (range 25 to 90) and was ≤40% in 8 patients. Of the 45 patients, 32 underwent revascularization with saphenous vein grafts alone, 3 had internal mammary grafts alone and 10 had combinations of graft conduits. A total of 87 vein grafts and 21 internal mammary artery grafts were placed. At the time of postoperative angiography, 27 saphenous vein grafts were completely occluded, 20 were stenosed and 40 were free of disease. Similarly, 3 internal mammary artery grafts were occluded proximally, 10 were stenosed at the distal anastomosis and 8 were patent. The major anatomic mechanism of recurrent ischemia for each patient is listed in Table I.

Results of angioplasty: An intraaortic balloon pump was used for severe hemodynamic instability in 3 patients (Table II). Coronary angioplasty was attempted at 98 sites with angiographic success in 91 (93%). Six of the 7 failures occurred before 1984 with nonsteerable equipment. In 18 patients, coronary angioplasty was performed within and through grafts only, in 12 patients angioplasty was performed in native arteries only and in the remaining 15 patients a combined strategy was used. In 22 patients, a bypassed artery was dilated through the native circulation owing to graft occlusion or stenosis. Of the 98 target sites, 41 were in native arteries, 46 were in vein graft conduits and 11 were in internal mammary arteries. In 8 patients treated before 1985, the operator elected to infuse 250,000 to 500,000 IU of streptokinase directly into a thrombosed vein graft. Seven of these 8 patients were among the emergent patients studied. Six of the 8 thrombosed bypass grafts were opened successfully with combined coronary angioplasty and thrombolytic agents. In the 25 patients treated since 1985, adjuvant thrombolytic agents were not used.

Complete revascularization was achieved in 38 patients (84%). Five of the 7 patients with incomplete revascularization were left with only total occlusions of the native right coronary artery. In the other 2, a circumflex artery and left anterior descending artery were left unrevascularized; the latter patient underwent bypass surgery before discharge.

Hospital course: Two hospital deaths (4%) occurred in the study group. One patient developed shock after occlusion of both saphenous vein grafts 6 days after CABG and died despite successful opening of both with coronary angioplasty and streptokinase. The other patient had successful elective coronary angioplasty of native right and circumflex coronary arteries 57 days after CABG. Four days later, sudden hemodynamic collapse occurred. Acute angiography revealed reocclusion of the

right coronary artery and new closure of a saphenous vein graft to the left anterior descending artery. Two patients (4%) had an increase in cardiac enzyme levels after coronary angioplasty without diagnostic Q waves. Two patients with unsuccessful coronary angioplasty underwent elective repeat CABG before discharge with uneventful recoveries. In total, complete procedural success was achieved in 34 patients (76%). All survivors were free of angina at discharge. Seventeen patients underwent predischarge exercise testing and all were free of angina.

Late follow-up: Follow-up status was determined for all 43 hospital survivors as of December 1989. The mean period of follow-up was 44 months (range 6 to 110) and was ≥24 months in 30 patients. During this period, 4 patients died. One patient died of respiratory failure 63 months after coronary angioplasty, 1 died of a stroke 5 months after angioplasty, 1 died of a myocardial infarction 59 months after angioplasty and 1 died of unknown causes 54 months after angioplasty. Late myocardial infarction occurred in 3 patients and was fatal in 1. Repeat CABG was required in 3 patients at 40, 58 and 66 months after the index coronary angioplasty. Repeat coronary angioplasty was performed in 10 patients, 2 of which were for new disease. Overall, 29 of 43 (67%) hospital survivors were free from all cardiac events during follow-up. Of the 39 patients alive at follow-up, 30 were in NYHA functional class I, 5 were in class II, 2 were in class III and 2 were in class IV. Seventeen patients continue to be employed full time.

DISCUSSION

Percutaneous transluminal coronary angioplasty and CABG offer alternative methods of myocardial revascularization. One perspective is that these 2 techniques are competitive and must be compared directly to one another.[17,18] In contrast, the patients in the present series demonstrate a complementary role of angioplasty and surgery not previously characterized: the relief of early postoperative myocardial ischemia with coronary angioplasty.

Mechanisms of ischemia: Although most patients treated for angina pectoris demonstrate rapid relief of symptoms after CABG,[1–4] improvement is not inevitable and the early return of angina is disappointing to patient and physician alike. Data from the Montreal Heart Institute demonstrate that between 8 and 14% of saphenous vein grafts close by 1 month after surgery as a consequence of graft thrombosis.[19] Even with uniform aspirin therapy, 7% of saphenous vein grafts may close an average of 9 days postoperatively, and 17% of patients have ≥1 occluded grafts.[20] Graft stenosis without occlusion can also lead to recurrent myocardial ischemia after CABG, and has been reported in 6 to 15% of all grafts soon after surgery.[19] Other mechanisms of recurrent symptoms include the presence of unbypassed coronary stenoses and disease distal to the insertion of grafts. Together, these mechanisms contributed to the restudy of 15% of our patients. Although internal mammary artery grafts have been advocated as the conduits of choice for their durability and relative freedom from late atherosclerosis,[21] this study demonstrates that they are not protected from early postoperative narrowing and closure.

Angioplasty after coronary artery bypass grafting: Reports from many medical centers demonstrate a considerable increase in the operative mortality for repeat CABG,[22–24] and alternative therapies with lower risks are attractive. Although an early report indicated a high procedural mortality rate associated with coronary angioplasty in patients with prior CABG,[25] many more recent and larger series of patients demonstrate its safety.[5–16] The angiographic success rate of 93% of lesions attempted in our patients is consistent with the 76 to 90% success rates reported in prior studies. The 2 procedural deaths in this selected series of patients represent a mortality rate that is somewhat higher than other series.[5–16] Both deaths occurred early in the series, with no deaths among the last 29 patients in the group.

Long-term outcome among the hospital survivors was excellent, with only 2 cardiac deaths occurring many years after coronary angioplasty. Repeat CABG could be avoided in all but 3 patients after discharge and the majority of patients were minimally symptomatic at last follow-up. As expected, repeat coronary angioplasty was required in a subset of patients (10 of 43) because of restenosis in 8 patients and new disease in 2 others.

Special considerations: Thrombosis of grafts is believed to be the major mechanism of early graft failure.[19,26,27] On many occasions we have succeeded in recanalizing acutely occluded vein grafts in the setting of acute myocardial infarction without thrombolytic therapy,[28] and succeeded with a similar approach in 6 of 8 acutely thrombosed grafts in this noninfarct series. Alternatively, adjunctive thrombolytic therapy delivered directly into the graft was also used early in our experience and has been reported to be effective by others.[8,29] Fewer patients with acutely thrombosed vein grafts were treated in the latter part of the series, perhaps reflecting uniform use of aspirin, improved surgical results or differences in patient selection. Our current approach is to attempt dilatations of acutely thrombosed vein grafts with balloon angioplasty alone, reserving thrombolytic drugs as "clean-up" agents if significant residual thrombus remains. Intragraft thrombolytic agents have been used in patients soon after CABG without complication.[30] Chronically occluded vein grafts are generally not dilated due to the low success rate and poor long-term patency. Dilating within a thrombosed graft can be avoided altogether by directing attention to sites of disease within native arteries. This strategy was used successfully in 22 patients and avoids the expense and risks of thrombolytic agents. Alternatively, chronic infusions of thrombolytic agents have been suggested for occluded vein grafts.[30,31]

We have not experienced complications of suture rupture in patients dilated as early as 2 days postoperatively and are not aware of reports of this occurring. Also, areas of recent anastomosis dilated well and the balloon was not constricted by tight sutures. Of course, care must be taken in balloon sizing and inflation pres-

sures used, limiting dilatations to pressures just adequate to relieve the narrowing in the balloon profile.

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Electrophysiologic and Electrocardiographic Effects, Efficacy and Safety of Encainide in Malignant Ventricular Arrhythmias Associated With Coronary Artery Disease

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The electrophysiologic and electrocardiographic effects, efficacy and safety of encainide were evaluated in 48 patients with coronary artery disease undergoing programmed stimulation for ventricular tachyarrhythmias. The study group included 41 men and 7 women, aged 64 ± 8 years (mean ± standard deviation), who had presented with nonsustained ventricular tachycardia (VT) (4 patients), sustained VT (32), ventricular fibrillation (8) or unexplained syncope (4). The left ventricular ejection fraction averaged 34 ± 13%. The arrhythmias induced at the baseline, drug-free electrophysiologic study included nonsustained VT in 8 patients, sustained VT in 35 and ventricular fibrillation in 5. All patients had failed ≥1 class IA and a combination of class IA and IB agents (mean 2.2 ± 1.1 drugs) before encainide. Oral encainide was given in a mean daily dose of 80 ± 11 mg for ≥3 days before repeat programmed stimulation. Encainide was discontinued before follow-up electrophysiologic testing in 5 patients due to spontaneous development of new sustained VT. Of the 43 patients undergoing electropharmacologic testing with encainide, 5 had no inducible arrhythmia. In 9 patients VT was inducible by fewer extrastimuli, in 2 patients a previously stable VT required cardioversion, whereas in 28 patients VT remained inducible by the same number of or more extrastimuli. Thus, encainide prevented the induction of VT or ventricular fibrillation in 5 of 48 patients (10%), while it had a possible proarrhythmic effect in 15 patients (31%). Of the 5 patients without inducible VT administered long-term encainide therapy, 1 returned within 4 weeks of hospital discharge with VT recurrence. Encainide has limited efficacy (10%) for prevention of ventricular arrhythmia induction by programmed stimulation, a high incidence of possible proarrhythmia (31%) and a late failure rate of 20% (1 of 5) despite noninducibility at electrophysiologic testing.

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Encainide, a benzanilide derivative, is a class IC antiarrhythmic drug recently approved for oral treatment of ventricular arrhythmias. During clinical investigation several studies demonstrated its efficacy for suppression of spontaneous ventricular tachyarrhythmias.[1–7] Subsequently, the efficacy of the drug in patients undergoing electrophysiologic evaluation has been investigated.[8,9] Since encainide was found to be associated with an increase in sudden death and total mortality in the Cardiac Arrhythmia Suppression Trial, its use has been restricted to patients with life-threatening ventricular arrhythmias.[10] The purpose of this study was to determine, using invasive evaluation, the electrophysiologic and electrocardiographic effects, efficacy and safety of encainide in a group of patients with coronary artery disease and these malignant ventricular tachyarrhythmias.

METHODS

Patients: The study population comprised 48 patients, 41 men and 7 women, aged 64 ± 8 (range 45 to 81) years (mean ± standard deviation), who were referred to our arrhythmia service for evaluation and management of symptomatic ventricular tachyarrhythmias or unexplained syncope (Table I). The presenting clinical arrhythmia was nonsustained ventricular tachycardia (VT) in 4 patients, sustained VT in 32 and ventricular fibrillation in 8. Four patients presented with unexplained syncope. All patients had underlying coronary artery disease; 4 patients with noncoronary disease, including 3 with idiopathic dilated cardiomyopathy, and 1 with sarcoid heart disease, were excluded from the study. Left ventricular ejection fraction, as assessed by echocardiography, radionuclide or contrast ventriculography, averaged 34 ± 13% and was ≤35% in 30 patients.

Electrophysiologic studies: All patients underwent baseline electrophysiologic studies in the fasting, nonsedated state. All antiarrhythmic drugs were discontin-

TABLE I Clinical Characteristics, Electrocardiographic and Electrophysiologic Effects of Encainide in 48 Patients with Coronary Artery Disease and Ventricular Tachyarrhythmias

					ECG				EPS		
Pt.	Age (yr) & Sex	LVEF (%)	CLIN ARRH	Prior Drugs	PR B/Rx	QRS B/Rx	QTc B/Rx	JTc B/Rx	VA B/Rx	CL B/Rx	VERP B/Rx
1	45 F	57	SYNC	Q, Q + Me	170/240	100/100	400/468	300/368	NSVT/SuVT	210/270	240/270
2	52 M	20	SuVT	Q, Q + Me	160/220	115/130	544/458	429/328	SuVT/SuVT	200/260	240/200
3	52 M	30	VT	Q, Q + Me	160/210	100/100	452/506	352/406	NSVT/NSVT	250/370	260/260
4	52 M	15	VT	Q, Q + Me	180/175	90/135	438/460	348/325	SuVT/SuVT	350/460	260/280
5	54 M	35	VT	Q, Q + Me	170/190	90/100	456/469	366/369	SuVT/SuVT	380/300	ND/300
6	54 M	23	VT	Q, Q + Me	190/200	100/100	422/456	322/356	SuVT/SuVT	230/250	300/270
7	55 M	60	NSVT	—	180/170	100/100	494/495	394/395	NSVT/NI	420/NI	270/260
8	55 M	55	VF	Q, Q + Me	140/170	70/70	423/414	353/344	SuVT/SuVT	210/240	230/250
9	55 M	35	NSVT	Q	240/150	170/180	410/434	240/254	SuVT/NI	240/NI	240/280
10	55 M	24	VT	A, A + Q	210/220	140/140	387/466	247/326	SuVT/SuVT	250/270	260/290
11	57 M	40	VT	Q, Q + Me	200/270	100/115	423/438	413/323	SuVT/SuVT	255/295	260/240
12	58 M	25	VT	Q, Q + Me, P, P + T	250/270	100/90	458/402	358/312	SuVT/SuVT	370/350	ND/260
13	59 M	55	VT	Q, P, Q + Me	100/230	90/110	452/477	362/365	VF/NSVT	—/310	220/290
14	59 M	50	VF	Q, Q + Me	150/210	90/80	490/550	400/470	SuVT/SuVT	250/340	230/320
15	59 M	40	NSVT	Q, A + P, Q + Me	220/160	100/100	512/400	412/300	SuVT/ND	400/Pr	290/ND
16	60 M	35	VF	Q	200/210	90/110	439/476	349/410	SuVT/SuVT	250/270	290/270
17	60 M	25	VT	P + Me, Fl + Me	170/160	110/125	429/494	319/369	SuVT/SuVT	230/240	ND/240
18	61 M	25	VF	Q + Me, P + T, P	160/170	150/160	435/455	285/295	SuVT/SuVT	225/270	ND/ND
19	61 M	35	VT	P, P + Me	270/NA	120/NA	471/NA	351/NA	SuVT/ND	250/Pr	240/ND
20	62 M	31	VT	Fl, Me, Me + N	150/220	100/160	488/516	388/356	SuVT/SuVT	310/270	250/250
21	63 M	25	VT	Q, Q + Me	210/270	130/110	566/445	430/335	SuVT/SuVT	245/350	280/260
22	64 M	25	VT	Q + Me	360/320	130/110	471/450	341/340	SuVT/SuVT	270/340	250/280
23	64 M	25	VT	Q, Q + Me	210/NA	90/NA	461/NA	371/NA	SuVT/ND	266/Pr	230/ND
24	66 M	30	VF	Q, Q + Me	180/220	100/150	413/465	313/315	SuVT/SuVT	300/250	280/260
25	66 M	55	SYNC	Q, Q + Me, Fl, T	165/160	90/100	410/440	320/340	NSVT/NSVT	200/270	290/280
26	67 F	20	VT	Q, Q + Me	200/280	115/160	540/483	425/323	SuVT/ND	290/Pr	240/ND
27	67 M	20	VT	T, T + Q	200/230	135/160	354/457	219/297	SuVT/SuVT	320/400	ND/ND
28	68 M	15	VT	—	230/230	70/100	418/454	348/354	NSVT/SuVT	200/230	230/260
29	68 F	25	VT	—	160/250	70/110	434/444	364/334	SuVT/SuVT	410/560	250/ND
30	69 M	15	VT	Q, Q + Me	220/270	100/120	437/460	337/340	NSVT/NSVT	210/350	220/ND
31	69 M	20	VF	—	140/180	80/110	377/416	297/306	VF/NSVT	—/200	ND/220
32	69 F	25	VT	Pir, Fl, Fl + T, A	200/150	90/120	426/504	336/384	NSVT/SuVT	250/500	250/320
33	69 M	40	VT	Q, Q + Me	130/220	95/90	453/458	358/368	SuVT/NI	200/NI	240/260

TABLE I (continued)

Pt.	Age (yr) & Sex	LVEF (%)	CLIN ARRH	Prior Drugs	ECG PR B/Rx	ECG QRS B/Rx	ECG QTc B/Rx	ECG JTc B/Rx	EPS VA B/Rx	EPS CL B/Rx	EPS VERP B/Rx
34	69 M	NA	VT	Q	250/ 280	140/ 100	446/ 450	306/ 350	SuVT/ SuVT	310/ 450	300/ 340
35	69 M	45	SYNC	—	200/ 215	110/ 120	395/ 457	285/ 337	VF/ SuVT	VF/ 280	260/ 240
36	70 M	47	SYNC	Q, Q + Me	200/ 240	160/ 130	434/ 471	274/ 341	SuVT/ NSVT	200/ 230	250/ 250
37	70 M	55	VT	Fl	160/ 220	75/ 115	440/ 490	365/ 375	NSVT/ SuVT	220/ 300	260/ 300
38	70 F	35	VF	Q, Q + Me	230/ 260	160/ 180	464/ 588	304/ 408	SuVT/ SuVT	300/ 330	260/ ND
39	70 M	20	VT	Q, Q + Me	230/ 180	70/ 70	560/ 390	490/ 320	SuVT/ NI	360/ NI	210/ 230
40	71 F	55	VT	Q	180/ 210	120/ 150	522/ 447	402/ 297	VF/ NI	—/ NI	250/ 240
41	71 M	35	VT	Q, Q + Me	AF/ 260	160/ 190	423/ 479	263/ 289	SuVT/ SuVT	250/ 350	260/ 270
42	72 M	45	VT	Q, Q + Me	190/ 230	110/ 125	434/ 464	324/ 339	SuVT/ SuVT	275/ 300	220/ 260
43	72 M	40	VT	Q, Q + Me	AF AF	150/ 160	400/ 460	250/ 300	SuVT/ SuVT	285/ 370	ND/ 250
44	73 F	45	VT	Q, Q + Me	180/ 230	100/ 130	396/ 425	296/ 295	SuVT/ SuVT	350/ 460	ND/ ND
45	73 M	22	VF	Q, Q + Me	170/ 250	100/ 120	396/ 452	296/ 332	VF/ SuVT	VF/ 330	240/ ND
46	76 M	30	VT	Q, Q + Me	230/ 320	100/ 140	433/ 490	333/ 350	SuVT/ SuVT	290/ 470	270/ ND
47	79 M	35	SuVT	P, Q + Me	AF/ AF	110/ 120	400/ 400	310/ 320	SuVT/ SuVT	270/ 430	250/ 250
48	81 M	20	VT	Q, Q + Me	210/ 220	80/ 120	420/ 410	340/ 290	SuVT/ ND	220/ Pr	260/ ND

A = amiodarone; AF = atrial fibrillation; B = baseline; CAD = coronary artery disease; CI = cycle length; CLIN ARRH = clinical arrhythmia; CM = cardiomyopathy; ECG = electrocardiogram; EPS = electrophysiologic study; F = female; Fl = flecainide; LVEF = left ventricular ejection fraction; M = male; Me = mexiletine; NA = not available; ND = not done or not determined; NI = noninducible; NSVT = nonsustained ventricular tachycardia; P = procainamide; Pir = pirmenol; Pr = proarrhythmia; Pt = patient; Q = quinidine; Rx = treatment; SHD = structural heart disease; SuVT = sustained ventricular tachycardia; SYNC = syncope; T = tocainide; VA = ventricular arrhythmia; VERP = ventricular effective refractory period; VF = ventricular fibrillation; VT = ventricular tachycardia; — = none, not available or not applicable.

ued for at least 5 drug half-lives before the study. Three quadripolar 6Fr electrode catheters were introduced through the femoral vein under local anesthesia using the Seldinger technique. Under fluoroscopic guidance the catheters were positioned in the high lateral right atrium, across the tricuspid valve for recording from the bundle of His and the right ventricular apex. Intracardiac recordings were filtered between 30 and 500 Hz and were displayed simultaneously with 3 surface electrocardiographic leads on a multichannel oscilloscope (Honeywell, Electronics for Medicine VR-12, Dedham, Massachusetts). All data were stored on a magnetic tape for subsequent analysis and were retrieved on photographic paper at speeds of 100 to 200 mm/s. Programmed cardiac stimulation was performed with a constant current stimulator (model 5328, Medtronic, Minneapolis, Minnesota), with rectangular pulses 2 ms in duration at 2 times the diastolic threshold.

The stimulation protocol[11] consisted of 1 and 2 extrastimuli during sinus rhythm, and 3 basic drive cycle lengths followed by 3 extrastimuli during sinus rhythm and ventricular pacing at the right ventricular apex and outflow tract. Left ventricular stimulation was not required in any patient. After the baseline study, serial electropharmacologic testing was undertaken in an attempt to find effective antiarrhythmic treatment. A drug was considered effective if at the follow-up study <6 beats of VT could be induced with the completion of the above stimulation protocol.

Encainide therapy: After the baseline study, the patients were tested first with a class IA antiarrhythmic agent and then with a combination of class IA plus IB agents, unless there was a history of clinical failure or adverse effect. The study group failed a mean of 2.2 ± 1.1 antiarrhythmic drugs before encainide was tested. Oral encainide was then administered in dosages of 25 to 50 mg (starting dose 25 mg) 3 times daily (mean daily dose 80 ± 11 mg) for ≥3 days before follow-up electrophysiologic study. Blood levels of encainide or its metabolites were not routinely monitored.

Clinical follow-up: Patients who had complete suppression of inducible VT with encainide were given long-term encainide therapy. They were followed up every 3 months with clinical evaluation and Holter or event monitors for adverse effects or any symptoms suggestive of arrhythmia recurrence.

Definitions: Sustained VT was defined as VT lasting >30 seconds or requiring intervention for hemodynamic compromise. Nonsustained VT was defined as VT of >5 consecutive beats but lasting <30 seconds. Clinical

criteria for proarrhythmic response to encainide include development of spontaneous sustained VT during drug evaluation in a patient who required programmed stimulation to initiate the arrhythmia at the baseline study. Electrophysiologic criteria for proarrhythmia during programmed stimulation include initiation of sustained VT with encainide in a patient in whom only nonsustained VT was provoked by the complete protocol during the baseline study. Additionally, induction of sustained VT or ventricular fibrillation during drug evaluation by fewer extrastimuli than at baseline was defined as a proarrhythmic response. Finally, conversion of a sustained VT that was terminated by programmed stimulation to a sustained arrhythmia requiring direct current cardioversion in a patient receiving encainide was also considered a proarrhythmic response.[12]

Statistics: Data are reported as mean ± standard deviation. Intergroup comparisons and evaluation of discrete variables were made by using Student's *t* test, Z-statistic or the chi-square test as appropriate. P values <0.05 were considered significant.

RESULTS

Baseline electrophysiologic studies: Of the 48 patients undergoing baseline programmed stimulation, 35 (73%) had inducible sustained VT, 8 (17%) had repro-

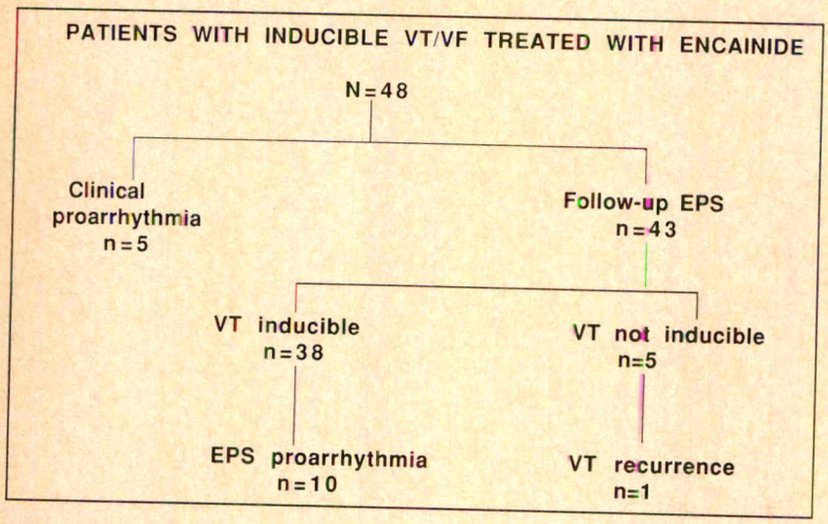


FIGURE 1. Electrophysiologic results and clinical outcome of encainide therapy in 48 patients with inducible ventricular tachycardia (VT) or ventricular fibrillation (VF) by programmed ventricular stimulation. EPS = electrophysiologic studies.

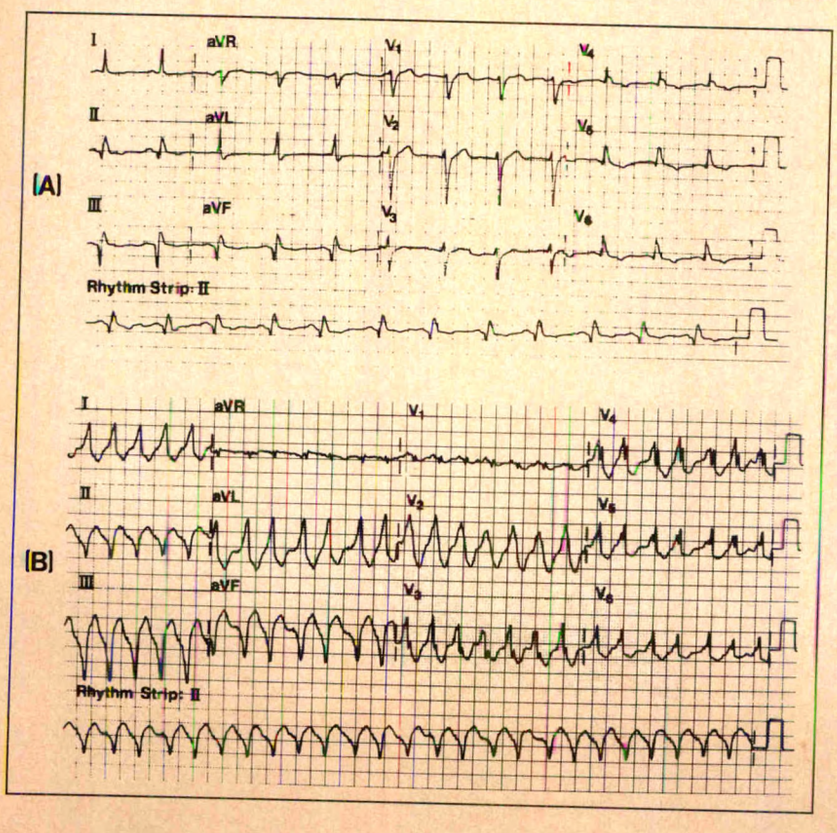


FIGURE 2. *A*, 12-lead ECG during encainide therapy in a patient with an old inferior wall myocardial infarction displays a sinus rhythm with a PR interval of 160 ms and a QRS duration of 130 ms. *B*, this patient, who had sustained VT that required programmed stimulation to induce, developed clinical proarrhythmia after 2 days of encainide therapy with spontaneous sustained VT, which was slow, recurrent and difficult to control.

ducible nonsustained VT and 5 had ventricular fibrillation. Ventricular arrhythmia was induced with programmed stimulation at the right ventricular apex using single extrastimuli in 4 patients (8%), double extrastimuli in 32 (67%) and triple extrastimuli in 10 (21%). Mean cycle length of the induced VT was 274 ± 62 ms. Single or double extrastimuli were used to terminate the induced sustained VT in 2 patients, rapid ventricular pacing was used in 15, and direct current cardioversion in 18.

Encainide therapy and follow-up electrophysiologic studies: Of the 48 patients who received loading with oral encainide, 5 patients (10%) developed spontaneous sustained VT within 3 days (Table I, Figures 1 and 2). Because this was considered a proarrhythmic effect (clinical proarrhythmia), encainide was discontinued before follow-up programmed stimulation. The other 43 patients underwent repeat programmed stimulation during encainide therapy. No arrhythmia was inducible at the follow-up study in 5 patients (10%). VT remained inducible with the same number of or more extrastimuli in 28 patients (nonsustained in 8 and sustained in 20). Arrhythmia was more easily inducible, requiring fewer extrastimuli, in 9 patients (Figure 3). In 2 patients, hemodynamically stable VT was induced in 1 with the same number of extrastimuli whereas it was more easily inducible in the other. It was terminated in both with programmed stimulation at baseline and required direct current cardioversion at the follow-up study. Mean cycle length of the induced VT increased significantly

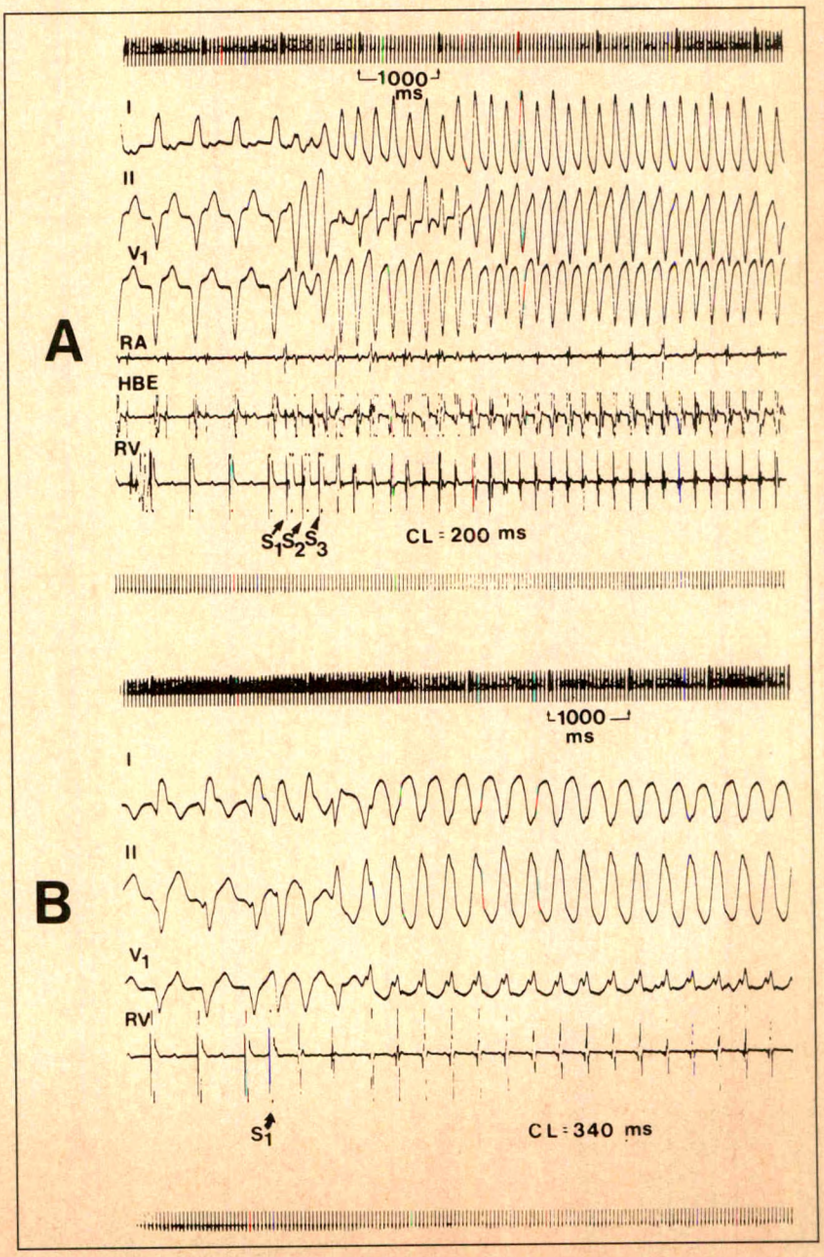


FIGURE 3. *A*, during baseline electrophysiologic study, sustained monomorphic VT with a cycle length (CL) of 200 ms and left bundle branch block-left axis morphology was induced with 3 extrastimuli ($S_1S_2S_3$) during ventricular pacing in 1 patient. *B*, at follow-up study during encainide therapy, sustained VT of different morphology (right bundle branch block-right axis) and slower CL (340 ms) is easily inducible with only 1 extrastimulus (S_1). Surface leads I, II and V_1 and intracardiac electrocardiograms from the high right atrium (RA), His bundle position (HBE) and the right ventricle (RV) are recorded.

from 274 ± 62 ms at baseline to 329 ± 85 ms with encainide (Figure 4); an increase of ≥100 ms was noted in 11 patients. Ventricular effective refractory period (253 ± 22 ms) did not significantly change with drug therapy (266 ± 29 ms) (Figure 4). Sustained VT was terminated with single or double extrastimuli in 7 patients, rapid ventricular pacing in 14 and cardioversion in 9.

Electrocardiographic effects of encainide: The PR interval increased from a mean baseline value of 194 ± 43 to 221 ± 43 ms ($p < 0.005$) with encainide therapy (Table I, Figure 5). The QRS complex also widened significantly from 108 ± 26 to 122 ± 28 ms ($p < 0.01$) with encainide. The QTc and JTc intervals, however, did not change significantly (445 ± 47 vs 461 ± 38 ms and 339 ± 55 vs 340 ± 39 ms, respectively).

Clinical follow-up: All 5 patients whose induced arrhythmias were suppressed by encainide during programmed stimulation were given long-term encainide therapy and were followed up clinically. However, 1 patient had late drug failure and returned to the hospital 2 weeks after discharge with spontaneous recurrence of sustained VT. At repeat programmed stimulation, VT was now inducible with encainide and drug therapy was

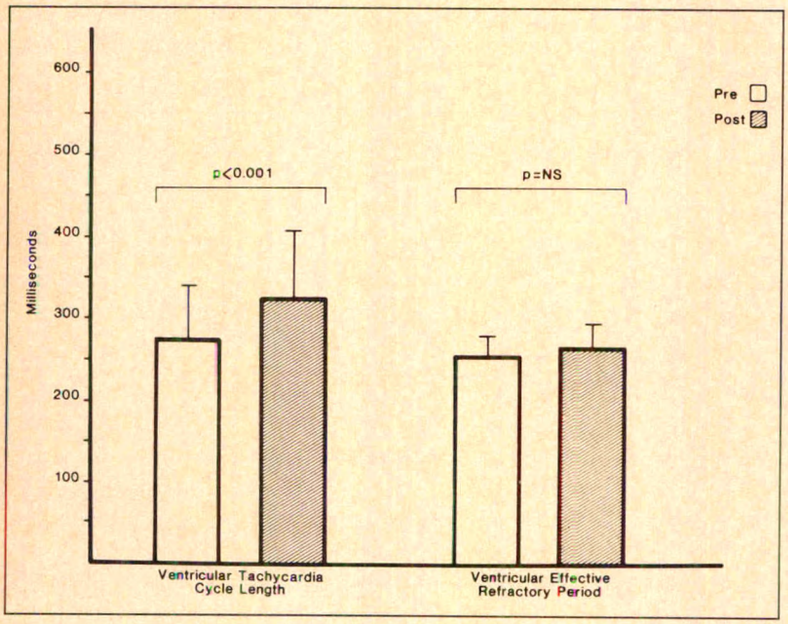


FIGURE 4. Encainide significantly slowed the rate of the induced ventricular tachycardia without changing the ventricular effective refractory period.

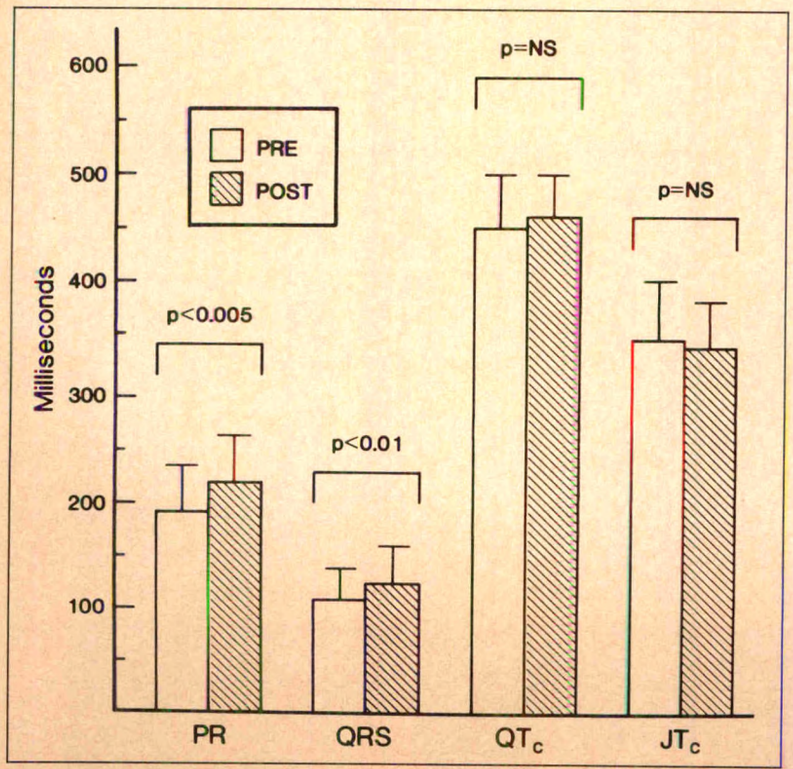


FIGURE 5. Electrocardiographic effects of encainide included a significant prolongation of PR interval and duration of QRS complex, but no effect on QTc and JTc intervals.

changed. In addition to having no inducible arrhythmias on electrophysiologic testing, this patient also had had negative (arrhythmia-free) Holter monitor and exercise tests while receiving encainide before hospital discharge. The remaining 4 patients (8%) continue to receive encainide at 5 to 15 months of follow-up without arrhythmia recurrence or significant adverse effects.

Proarrhythmia: In all, a proarrhythmic response to encainide was observed in 15 patients (31%) (Figure 1). It occurred in 5 spontaneously (Figure 2) and 10 met criteria for proarrhythmic response during programmed stimulation. Of the 10, 9 had VT induced with fewer extrastimuli (Figure 3) (1 of whom also had conversion of a hemodynamically stable VT into unstable VT, requiring cardioversion), and 1 had previously stable VT induced with the same number of extrastimuli that required follow-up study cardioversion for termination.

Influence of clinical, electrocardiographic and electrophysiologic variables on drug efficacy and proarrhythmia: A series of clinical, electrocardiographic and electrophysiologic variables were examined as predictors of proarrhythmia or efficacy. These parameters included age (> or <60 years), gender, clinical sustained versus nonsustained arrhythmia, history of cardiac arrest, baseline duration of QRS complex (> or <160 ms), number of prior drug failures, mode of induction, rate of induced VT at baseline electrophysiologic study and degree of left ventricular dysfunction (ejection fraction > or <35%). Univariate analysis failed to show any predictive value of these variables for either proarrhythmia or efficacy.

DISCUSSION

The efficacy of encainide for prevention of ventricular tachyarrhythmia induction by programmed stimulation was limited to 10% in the present study. During clinical follow-up, this percentage decreased to 8%. Although this efficacy rate is low compared with that reported by other investigators in earlier studies,[1,2,8] it is comparable to more recent reports.[9] In the Encainide-Ventricular Tachycardia Study Group,[9] there were only 14 of 94 patients (15%) whose inducible sustained VT became noninducible with encainide. In that study, a partial response, defined as an increase in the VT cycle length and as the absence of hemodynamic symptoms compared with the tachycardia in the baseline study, was also considered an acceptable response, raising the overall success rate of encainide therapy to 34%. However, among the patients with partial response, 39% had recurrence of VT compared with only 7% of the noninducible group during long-term follow-up. In our study no patient with VT still inducible was discharged receiving encainide, although 11 patients with VT slowing (≥100 ms) met the criteria for a "partial" response. However, of the 5 patients with no inducible arrhythmia while receiving encainide, 1 had arrhythmia recurrence.

This study also reports a high rate (31%) of possible proarrhythmia noted with encainide among patients with life-threatening ventricular tachyarrhythmias. The high proarrhythmia incidence in this study is related to the broad clinical and electrophysiologic definitions used. These criteria for proarrhythmia, proposed by Horowitz,[12] have not been evaluated in prospective trials. The inability of encainide to prevent spontaneous or induced VT in the patients included in the proarrhythmia group at least precluded long-term encainide therapy. In contrast to previous studies with class IC agents,[13–15] the degree of left ventricular dysfunction was not predictive of an increased incidence of proarrhythmia in the present study. Furthermore, neither drug failure nor proarrhythmia could be predicted by any other clinical, electrophysiologic or electrocardiographic variable.

The multiple initial studies[3,5,6] of the acceptable efficacy and safety of encainide for suppression of spontaneous arrhythmias in patients with benign or potentially lethal arrhythmias were corroborated by data from the Cardiac Arrhythmia Pilot Study.[7] Despite suppression of spontaneous arrhythmias, encainide has recently had its use limited in these patients because of an almost 3-fold increase of total mortality and nonfatal cardiac arrest, from 3.6% (15 of 416) in the matched placebo group to 9.6% (40 of 415) in patients randomized to encainide in the Cardiac Arrhythmia Suppression Trial.[10] Using programmed ventricular stimulation in a population of patients with coronary artery disease and life-threatening ventricular tachyarrhythmias, including sustained VT and ventricular fibrillation and symptomatic nonsustained VT, encainide has low efficacy and a high incidence of proarrhythmia.

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Role of Alcohol in Recurrences of Atrial Fibrillation in Persons <65 Years of Age

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The role of alcohol in recurrences of atrial fibrillation (AF) was assessed in a consecutive series of 98 patients (75 men) aged <65 years. In addition to etiologic assessment using clinical and laboratory methods and echocardiography, the patients' drinking habits were evaluated by recording the amount of alcohol used during the week preceding AF, by responses to the CAGE (Cut, Annoying, Guilt, Eye; see below) questionnaire (a screening test for alcohol abuse) and by selected laboratory tests. Two groups of control subjects were studied: 98 sex- and age-matched patients admitted to the emergency ward for acute illnesses, and 50 subjects selected randomly from the local out-of-hospital population. The mean alcohol consumption among men during the study week was 186 g (median 45 g; range 0 to 2,100 g) among patients, whereas among male hospital and population control subjects it was 86 g (30 g; 0 to 1,050 g) and 94 g (35 g; 0 to 630 g), respectively. When the weekly alcohol consumption was analyzed in 3 categories (0; 1 to 210 g; >210 g), there was a significant difference between AF cases and hospital control patients ($p = 0.03$), but not between AF cases and population control subjects. Multivariate analysis of data of AF cases and population control subjects showed that alcohol intake and a positive response to 1 or more of the CAGE questions were independently related to AF in men. Other independent risk factors were the presence of heart disease, low serum potassium and lack of sleep or experience of excess psychologic stress, or both. These results indicate that alcohol consumption is an independent risk factor for recurrences of AF in men of working age.

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Alcohol has been claimed to induce cardiac arrhythmias by causing subclinical or overt cardiomyopathy,[1,2] changing conduction times and refractory periods in the myocardium,[3–5] provoking abrupt increases in vagal tone and increasing circulating catecholamines.[6] Previous reports have suggested that alcohol, often acting with exceptional mental stress and lack of sleep, can provoke arrhythmias, especially atrial fibrillation (AF), even in otherwise healthy persons.[7–13] None of the earlier clinical studies has, however, assessed the role of alcohol as an independent risk factor for AF, and in none of them has a proper population control group been studied.

We have previously shown that the recent alcohol intake of patients presenting with their first episode of AF, and especially of men with idiopathic AF, was significantly higher that that of age- and sex-matched hospital derived control subjects.[14] To further evaluate the relation between alcohol and AF, we studied young and middle-aged patients with recurrent AF and compared their drinking habits and other lifestyle data with those of matched control patients from the hospital and with those of a group of population control subjects. In addition, we performed multivariate analyses on probable underlying and precipitating factors of AF.

METHODS

Patients: A consecutive series of 98 patients (<65 years of age) with recurrent AF was collected during an 8-month period in the emergency department of a university hospital (catchment population approximately 900,000). All patients had to have had at least 1 prior electrocardiographically documented episode of AF.

Etiologic evaluation of atrial fibrillation: The AF patients were examined on the day of admission or the next morning when most patients had reverted to sinus rhythm. Cardiac and noncardiac diseases were identified by medical history, results of previous cardiac examinations, clinical examination, chest x-ray, 12-lead electrocardiogram, laboratory tests and lung function tests (when necessary).[14] The diagnostic criteria for the underlying diseases were the same as in our previous investigation.[14] A combined 2-dimensional and M-mode echocardiographic study (Toshiba SSH 60A) was performed if the clinical assessment did not reveal any underlying factor for the current episode of AF.[15]

Evaluation of drinking habits and other lifestyle data: After informed consent, the patients were interviewed by one of us (P.K.), usually within 12 hours after admission. The amounts and types of alcoholic bev-

erages they had consumed during the week preceding the onset of AF were recorded and converted into grams of absolute alcohol. The patients were asked also whether this consumption had been higher, lower or the same as normally. They were also given the 4 CAGE questions: Have you ever felt you should Cut down on your drinking? Have people Annoyed you by criticizing your drinking? Have you ever felt bad or Guilty about your drinking? Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (Eye-opener)?

Coffee drinking and smoking habits were recorded, as well as history of sleeping patterns (During the week preceding the arrhythmia, have you slept less than normally?) and feelings of emotional and mental stress at work or in private life (During the week preceding the arrhythmia, did you experience more emotional or mental stress, either at home or at work, than normally?).

Control subjects: After the patient with AF had been identified, an age- (±10 years) and sex-matched control patient was selected from the contemporary list of the emergency ward patients. The control group comprised patients with acute illnesses, largely people with lung and abdominal diseases. We excluded subjects with clearly alcohol-related illnesses, such as acute pancreatitis or drug intoxications, as well as those who had been admitted because of a chronic debilitating disease, such as cancer. Patients with angina were excluded also. After informed consent, each control patient was interviewed identically to the AF case. No systematic laboratory tests were done on them.

We also studied a sample of individuals from the out-of-hospital population. The Central Office of Statistics gave us a list of names, addresses and birthdays of randomly chosen people (23 to 65 years of age) from the catchment area of our hospital. Fifty-three of them were contacted by letter and later by telephone and, when willing to participate, given an appointment time to visit the cardiovascular laboratory. In choosing these control subjects our only criterion was to form a group that would be similar to the AF population in age and sex distribution. Those 50 who consented (94%) underwent the same interviews and examinations as the AF patients, including echocardiography. The week relating to their alcohol consumption and other lifestyle data was the week preceding the telephone call.

Statistical analysis: The statistical analyses were done using BMDP software.[16] When comparing alcohol consumption and other questionnaire data between AF patients and matched hospital control patients, McNemar's test of symmetry was used. Univariate analyses of the data of randomly selected population control subjects and AF patients were performed with the 2-tailed Fisher's exact test (2 × 2 tables) and the G^2 likelihood ratio test (2 × 3 tables). Stepwise logistic regression (maximum likelihood method) was used in multivariate analyses. Because of the skewness of the alcohol consumption data, the medians and ranges are given in addition to the means. A p value <0.05 was considered statistically significant.

TABLE I Diseases Associated with Recurrent Atrial Fibrillation

Diseases	No. of Pts.
Coronary artery disease	
Prior myocardial infarction	16
Angina pectoris on effort	12
Total	28*
Systemic hypertension	17
Mitral valve disease	
Rheumatic	6
Prolapse	1
Total	7
Cardiomyopathy	
Hypertrophic	4
Dilated	1
Total	5
Chronic obstructive pulmonary disease	3
Atrial septal defect	2
Prior myopericarditis	2
Aortic valve stenosis	1
Aortic coarctation	1
Sick sinus syndrome	1
Preexcitation syndrome	1
Obesity-related heart disease	1
Myotonic muscular dystrophy	1
Radiation-induced heart disease	1
Prior knife wound in pericardium	1
Prior heart contusion	1
Idiopathic	25

* Six also had hypertension.

RESULTS

The group of AF patients consisted of 75 men and 23 women. The mean age of cases and matched hospital control patients was 52 (range 22 to 64) and 51 (22 to 67) years, respectively. There were 38 men and 12 women among the population control subjects; their mean age was 51 years (31 to 64).

Diseases associated with atrial fibrillation and their prevalence in the population sample: The diseases or conditions considered etiologically associated with AF are listed in Table I. Among the 50 population control subjects, 6 had systemic hypertension, 3 coronary artery

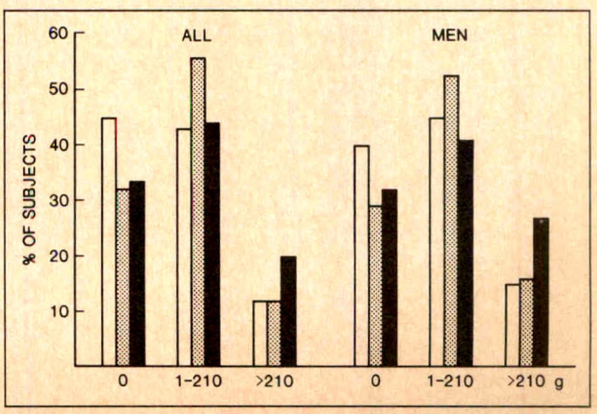


FIGURE 1. The distribution of patients with atrial fibrillation (*black columns*), matched control patients (*white columns*) and randomly selected population control subjects (*grey columns*) in 3 categories of alcohol consumption (g of alcohol/week).

TABLE II Subjects' Own Estimation of Their Alcohol Intake During the Study Week as Compared with Their Normal Drinking

Group	Alcohol Intake			
	More	Less	Same	χ^2/p*
All subjects				
Atrial fibrillation (n = 98)	27	4	69	
Matched controls (n = 98)	17	1	82	6.24/0.10
Population controls (n = 50)	10	6	84	6.08/0.048
Men				
Atrial fibrillation (n = 75)	32	5	63	
Matched controls (n = 75)	17	1	82	9.09/0.03
Population controls (n = 38)	11	5	84	7.05/0.03

* χ^2/p gives the chi-square value and the associated p value as compared with the atrial fibrillation group.
The numbers are percentages.

TABLE III Frequency (%) of Subjects Responding Affirmatively to 1 or More, or to All of the CAGE Questions

Group	Responses to the CAGE Questions			
	≥1 Positive	p Value*	4 Positive	p Value*
All subjects				
Atrial fibrillation (n = 98)	35		12	
Matched controls (n = 98)	29	0.32	9	0.47
Population controls (n = 50)	28	0.46	2	0.06
Men				
Atrial fibrillation (n = 75)	45		16	
Matched controls (n = 75)	36	0.24	12	0.47
Population controls (n = 38)	34	0.31	0	0.008

* Significances as compared with the atrial fibrillation group.

TABLE IV Abnormal Laboratory Values Among Patients with AF and Among Population Control Subjects

	AF Patients (n = 98)	Controls (n = 50)	p Value
MCV >96 fl	18% (8/44)	5% (2/42)	NS
GGT >50 UI/liter	29% (25/87)	6% (3/47)	<0.001
ASAT >40 UI/liter	14% (12/86)	8% (4/48)	NS
>80 UI/liter	1% (1/86)	2% (1/48)	NS
ALAT >40 UI/liter	26% (23/90)	8% (4/49)	<0.05
>80 UI/liter	7% (6/90)	6% (3/49)	NS
Potassium <3.7 mmol/liter	31% (29/95)	0% (–/49)	<0.001
<3.0 mmol/liter	5% (5/95)	0% (–/49)	NS
Calcium <2.25 mmol/liter	34% (31/91)	2% (1/48)	<0.001
Phosphate <0.80 mmol/liter	17% (15/88)	2% (1/48)	<0.01
Magnesium <0.70 mmol/liter	6% (5/88)	4% (2/46)	NS
Albumin <34 g/liter	7% (6/87)	6% (3/47)	NS

The figures in parentheses denote number of abnormal values/number of patients tested.
AF = atrial fibrillation; ALAT = serum alanine aminotransferase; ASAT = serum aspartate aminotransferase; GGT = serum gamma-glutamyl transpeptidase; MCV = erythrocyte mean corpuscular volume (electrolytes and albumin were determined from serum samples); NS = not significant.

disease and 2 chronic obstructive pulmonary disease. Mitral valve prolapse and hypertrophic cardiomyopathy were both diagnosed in 1 subject. One subject had left bundle branch block without any other sign of cardiovascular disease, 3 men had had episodes of AF and 1 young woman had had episodes of supraventricular tachycardia. One otherwise healthy man had chronic AF.

Univariate analyses of alcohol consumption: The mean alcohol consumption during the week in question was 147 g (median 30 g; range 0 to 2,100 g) among the AF patients. The matched control patients and the population control subjects had consumed on the average 77 g (15 g; 0 to 1,050 g) and 81 g (30 g; 0 to 630 g), respectively. The corresponding figures for men only were 186 g (45 g; 0 to 2,100 g) for AF cases, and 86 g (30 g; 0 to 1,050 g) and 94 g (35 g; 0 to 630 g) for the hospital and population control subjects, respectively. The mean consumption in the group of 20 men with idiopathic AF was 355 g of ethanol (180 g; 0 to 2,100 g). Figure 1 shows the distribution of cases and control subjects in 3 categories of alcohol consumption (0, 1 to 210 g and >210 g of ethanol/week). There was a statistically significant difference between all cases and matched control subjects (chi-square = 8.76; p = 0.03), but not between cases and population control subjects (chi-square = 2.55; p = 0.28). This was also true when men were analyzed separately; the difference between cases and matched control subjects was significant (chi-square = 9.02; p = 0.03), whereas that between cases and population control subjects was not (chi-square = 2.49; p = 0.29). There were no significant differences in alcohol consumption between women with AF and either of the 2 control groups.

The subjects' own estimates of how the alcohol consumption during the week in question agreed with their normal drinking are listed in Table II. The frequencies of subjects responding affirmatively to 1 or more of the CAGE questions and the frequencies of those giving positive answers to all 4 questions are listed in Table III. Importantly, 4 AF patients and 3 matched control subjects gave a positive answer to all questions but denied drinking any alcohol during the week in question. In the group of 20 men with idiopathic AF, 70% answered affirmatively to 1 or more of the questions, and 20% to all of them.

Blood ethanol concentration was obtained in 64 AF patients on admission. In 14% of them, it exceeded 10 mmol/liter and in 19%, 1 mmol/liter.

Other questionnaire data: The proportion of current smokers was 29% among AF cases, 31% among matched control patients and 38% among population control subjects, and 84, 83 and 88%, respectively, drank coffee daily.

Thirty-seven percent of AF patients and 20% of random control subjects (p = 0.04) reported that their life during the study week had been more stressful than usually, and 41% of patients but only 22% of control subjects (p = 0.03) said they had slept unusually badly. The frequencies of those with excess stress or poor sleeping, or both, in the matched hospital control patients were 28 and 34%, respectively. These were not significantly different from the frequencies in the AF patients.

Laboratory data: Table IV lists laboratory data of AF patients and population control subjects. Five men

TABLE V Logistic Regression Coefficients (b), Improvement Chi-Square Values and Their Significances in Analyses of Data of Patients with AF and Population Control Subjects

Variable	All Subjects (n = 144)		Men (n = 110)	
	b (SE)	Chi-Square	b (SE)	Chi-Square
Model I				
Serum potassium	−1.96 (0.53)	22.57*	−1.42 (0.58)	11.99†
Associated disease	2.17 (0.46)	20.05*	2.06 (0.52)	12.41*
Stress or lack of sleep	0.92 (0.50)	3.57	1.43 (0.64)	5.69‡
Amount of alcohol	0.0019 (0.0012)	3.61	0.0020 (0.0012)	3.99‡
Constant	7.05 (2.17)		4.80 (2.43)	
Model II				
Serum potassium	−1.99 (0.53)	22.57*	−1.40 (0.58)	11.99†
Associated disease	2.30 (0.49)	20.05*	2.28 (0.57)	12.41*
Stress or lack of sleep	1.01 (0.51)	3.34	1.57 (0.66)	5.69‡
CAGE (≥1 positive)	0.97 (0.51)	3.90‡	1.18 (0.58)	4.61‡
Constant	7.03 (2.20)		4.40 (2.50)	

* $p < 0.001$; † $p < 0.01$; ‡ $p < 0.05$.
AF = atrial fibrillation; Amount of alcohol = amount of alcohol (g/week) consumed during the week preceding investigations; Associated disease = disease etiologically associated with AF (yes/no); CAGE (≥1 positive) = 1 or more affirmative responses to the questionnaire detecting alcohol abuse (yes/no); SE = standard error; Stress or lack of sleep = feeling of unusual stress or lack of sleep, or both, during the week preceding the investigations (yes/no).

with AF, but none of the random control subjects, had both red cell mean corpuscular volume and gamma-glutamyl transpeptidase values above normal ($p = 0.01$). Among men with idiopathic AF, 33% of those tested had serum gamma-glutamyl transpeptidase value above normal. None of the patients or the control subjects had abnormally high serum thyroxine levels.

Multivariate analysis of data of atrial fibrillation patients and population control subjects: Stepwise logistic regression was performed with AF+ and AF− as the dependent variable. The independent variables in the final analyses were serum potassium (mmol/liter) and alcohol consumption (g/week) as continuous variables, and associated disease (0 = no disease; 1 = any associated disease), CAGE questionnaire response (0 = no positive responses; 1 = 1 or more positive response) and the combination of stress and lack of sleep (0 = both negative; 1 = either or both positive) as dichotomized variables. The amount of alcohol and the CAGE questionnaire responses were included interchangeably in the model. The analyses were carried out separately for all subjects and men alone. Table V gives the logistic regression coefficients and the improvement chi-square values for each independent variable.

DISCUSSION

These data show that in young and middle-aged patients with recurrent AF, particularly in men, both recent and chronic alcohol use play a significant role in the onset of the arrhythmia. These findings agree well with our previous study of patients with new-onset AF,[14] with earlier retrospective clinical investigations[12,13] and with the newest prospective epidemiologic data.[17]

Problems in selecting control subjects in alcohol research: All comparable previous controlled studies have used control groups consisting of hospital patients.[12–14] However, such people may not always be representative of the general population because patients attending emergency departments clearly include an excess of problem drinkers.[18,19] We tried to avoid overrepresentation of heavy drinkers among the hospital control subjects by excluding patients with clearly alcohol-related diseases, a practice commonly used in noncardiac alcohol studies as well.[20,21] On the other hand, we also excluded patients whose alcohol use was supposedly minimal. To further minimize the possible bias due to the selection of control subjects, we studied a random sample of the out-of-hospital population. This enabled us to perform multivariate analyses that showed for the first time that, even when adjusting for such confounding factors as AF-related diseases, low serum potassium and stress and lack of sleep, recent alcohol consumption was associated with the onset of AF, at least in men.

Problem drinking and atrial fibrillation: The CAGE questionnaire is a specific and sensitive screening test for alcohol abuse,[22] although it cannot distinguish between recent and past heavy drinking. The sensitivity and specificity for alcohol abuse of 1 or more positive responses in the study by Bush et al[22] were 85 and 89%, respectively, and if all 4 responses were positive, the specificity increased to 100%. The frequencies of positive responders in our 2 control groups are well in accord with the results of that particular investigation. It is noteworthy that we found a significant difference between the male AF patients and population control subjects in the number of problem drinkers (that is, in those giving affirmative responses to all 4 questions). This finding gains support from the laboratory data, which showed significantly more AF patients than population control subjects having both macrocytosis and high gamma-glutamyl transpeptidase values. Together these observations strongly suggest an association between problem drinking and recurrent AF in men. The lack of association of alcohol intake and AF in women was most likely due to the small number of women among the patients, although there are earlier data suggesting a sex difference in the cardiac effects of alcohol.[23]

Stress and atrial fibrillation: In many case reports of patients with paroxysmal AF,[7–11] excessive mental stress has been one of the most commonly reported pre-

cipitating factors, often in conjunction with heavier than normal alcohol use. However, the role of stress has not previously been evaluated using appropriate control groups. Our data suggest that psychological stress has, indeed, a role in the onset of AF. The limitations of our study to evaluate stress must be recognized, however. First, our primary objective was not to examine the role of stress in recurrences of AF, and second, we did not, for example, measure the anxiety score with a structured and validated questionnaire but recorded instead the patients' subjective estimates. Nevertheless, the results indicate that the patients had frequently experienced unusual psychologic stress before the onset of AF, and that this was associated with the recurrence of AF independently of the other risk factors assessed.

Factors underlying atrial fibrillation: Our data and other recent studies[14,24] show coronary artery disease and systemic hypertension to be by far the most common conditions associated with paroxysmal AF today. Rheumatic mitral valve disease has become a relatively rare entity and hyperthyroidism seems to be of no significance to recurrent AF. Hypokalemia was a relatively common finding in our AF patients and serum potassium was in fact the factor most strongly associated with AF in multivariate analysis. Mild hypocalcemia was surprisingly common among the AF patients, even despite normal serum albumin values. The pathogenetic role of hypocalcemia in AF is poorly known, however, and must be studied more before any firm conclusions can be made of our data.

Conclusions: Self-reported alcohol consumption was significantly higher among 98 patients with recurrent AF than among matched hospital control subjects. AF patients had also consumed more alcohol than randomly selected individuals from the out-of-hospital population, but this difference was not statistically significant. The CAGE questionnaire, however, uncovered significantly more problem drinkers among the male AF patients than among the population control subjects. Heavy drinkers were often men with idiopathic AF. Multivariate analysis showed that, among men, both self-reported alcohol consumption and 1 or more positive responses to the CAGE questions were risk factors for AF independent of associated diseases, hypokalemia and excessive stress or lack of sleep.

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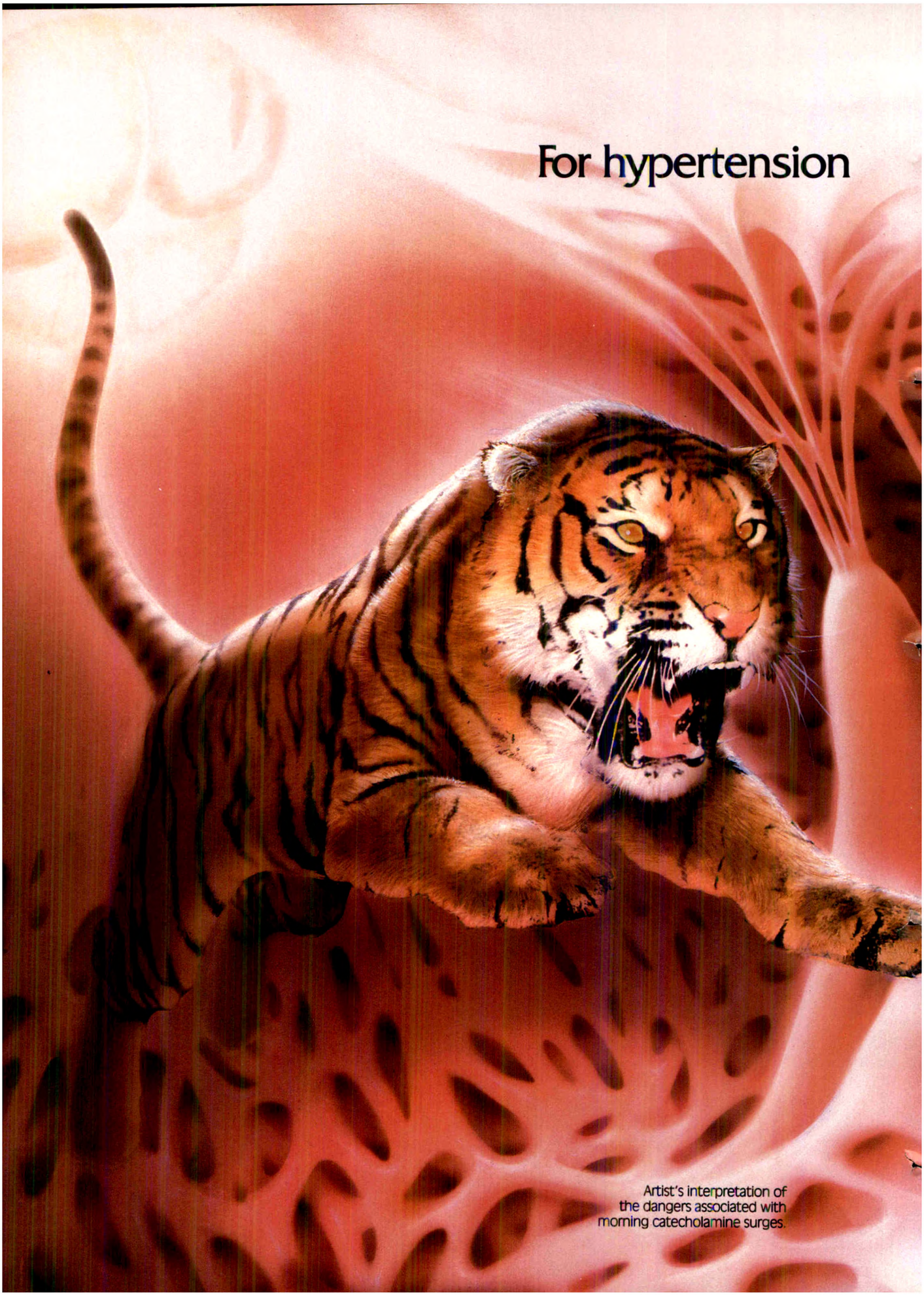
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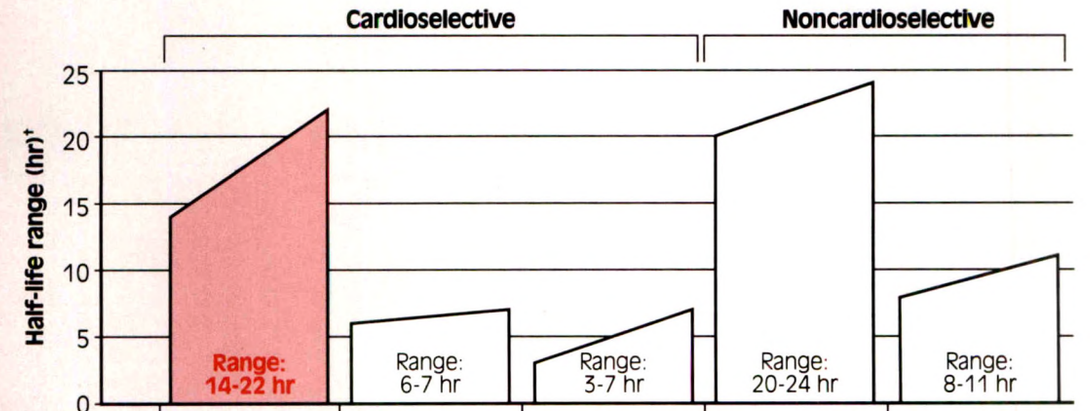
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*Refers to catecholamines, norepinephrine and epinephrine, serum concentrations of which may increase two- to threefold in the morning compared with trough levels (Reference: Tofler GH, Brezinski D, Schafer AI, et al: Concurrent morning increase in platelet aggregability and the risk of myocardial infarction and sudden death. *N Engl J Med* 1987;316:1514-1518.)

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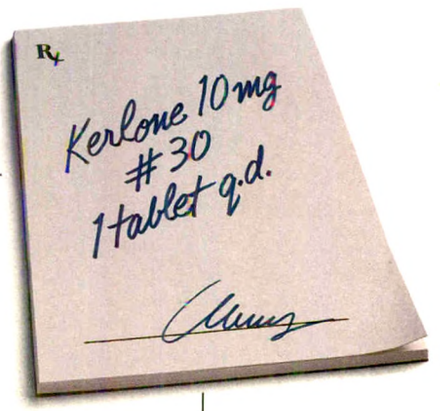
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References:

1. Kerlone complete prescribing Information. **2.** Data on file, G.D. Searle & Co.
3. *Drug Topics® Red Book*, ed 94. Oradell, NJ, Medical Economics Co Inc, April 1990.

BRIEF SUMMARY

Contraindications: Known hypersensitivity to the drug, sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see *Warnings*).

Warnings: In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, beta-blockers should be administered cautiously. At the first sign or symptom of cardiac failure, discontinuation of Kerlone should be considered. In some cases Kerlone can be continued while cardiac failure is treated with cardiac glycosides, diuretics, and other agents, as appropriate. Abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease has been followed by exacerbations of angina pectoris and, in some cases, myocardial infarction has been reported; patients should be warned against interruption of therapy without the physician's advice. When discontinuation of Kerlone is planned, the patient should be carefully observed and therapy should be reinstituted, at least temporarily, if withdrawal symptoms occur. **PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD NOT IN GENERAL RECEIVE BETA-BLOCKERS. Because of its relative β_1 selectivity, low doses of Kerlone may be used with caution in patients with bronchospastic disease who do not respond to or cannot tolerate alternative treatment. Since β_1 selectivity is not absolute and is inversely related to dose, the lowest possible dose of Kerlone should be used (5 to 10 mg once daily) and a bronchodilator should be made available. If dosage must be increased, divided dosage should be considered to avoid the higher peak blood levels associated with once-daily dosing.** The risk of excessive myocardial depression during general anesthesia may be increased and difficulty in restarting and maintaining the heart beat has been reported with beta-blockers. If treatment is continued, particular care should be taken when using anesthetic agents which depress the myocardium, and it is prudent to use the lowest possible dose of Kerlone. Beta-blockers should be used with caution in diabetic patients as they may mask tachycardia occurring with hypoglycemia (patients should be warned of this), although other manifestations such as dizziness and sweating may not be significantly affected. Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism. Abrupt withdrawal might precipitate a thyroid storm; therefore, patients known or suspected of being thyrotoxic from whom Kerlone is to be withdrawn should be monitored closely.

Precautions: Beta-adrenoceptor blockade can cause reduction of intraocular pressure. Since betaxolol hydrochloride is marketed as an ophthalmic solution for treatment of glaucoma, patients should be told that Kerlone may interfere with the glaucoma-screening test. Withdrawal may lead to a return of increased intraocular pressure. Patients receiving beta-adrenergic blocking agents orally and beta-blocking ophthalmic solutions should be observed for potential additive effects. Kerlone clearance is somewhat reduced in patients with renal failure but little changed in patients with hepatic disease. Dosage reductions have not routinely been necessary when hepatic and/or renal insufficiency is present but patients should be observed. Patients on dialysis require a reduced dose. Patients should be warned against interruption or discontinuation of Kerlone therapy without the physician's advice. Patients being treated with beta-adrenergic blocking agents should be advised to consult a physician at the first sign or symptom of cardiac failure. Patients should know how they react to this medicine before they operate automobiles and machinery or engage in other tasks requiring alertness; contact their physician if any difficulty in breathing occurs, and before surgery of any type; and inform their physicians or dentists that they are taking Kerlone. Patients with diabetes should be warned that beta-blockers may mask tachycardia occurring with hypoglycemia. Patients treated with a beta-adrenergic receptor blocking agent plus a catecholamine depletor should be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension. When discontinuing therapy in patients receiving beta-blockers and clonidine concurrently, the beta-blocker should be discontinued slowly over several days before the gradual withdrawal of clonidine. Literature reports suggest that oral calcium antagonists may be used in combination with beta-adrenergic blocking agents when heart function is normal, but should be avoided in patients with impaired cardiac function. Hypotension, AV conduction disturbances, and left ventricular failure have been reported in some patients receiving beta-adrenergic blocking agents when an oral calcium antagonist was added to the treatment regimen. Hypotension was more likely to occur if the calcium antagonist were a dihydropyridine derivative, eg, nifedipine, while left ventricular failure and AV conduction disturbances, including complete heart block, were more likely to occur with either verapamil or diltiazem. Pregnancy Category C. In a study in which pregnant rats received betaxolol, the highest dose (600 X MRHD) was associated with increased postimplantation loss, reduced litter size and weight, and an increased incidence of skeletal and visceral abnormalities, which may have been a consequence of drug-related maternal toxicity. Other than a possible increased incidence of incomplete descent of testes and sternebral reductions, betaxolol (6 X MRHD and 60 X MRHD) caused no fetal abnormalities. In a second study with a different strain of rat, betaxolol (300 X MRHD) was associated with maternal toxicity and an increase in resorptions but no teratogenicity. In a study in which pregnant rabbits received betaxolol (54 X MRHD), a marked increase in postimplantation loss occurred at the highest dose. In a peri- and postnatal study in rats, betaxolol (380 X MRHD) was associated with a marked increase in total litter loss within 4 days postpartum. In surviving offspring, growth and development were also affected. There are no adequate and well-controlled studies in pregnant women. Kerlone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Since Kerlone is excreted in human milk caution should be exercised when Kerlone is administered to a nursing mother. Safety and efficacy in children have not been established. Kerlone may produce bradycardia more frequently in elderly patients.

Adverse Reactions: Kerlone has been associated with the development of antinuclear antibodies (5.3%). Betaxolol adverse events reported in U.S. controlled studies: bradycardia (8.1), symptomatic bradycardia (0.8), edema (1.8), headache (6.5), dizziness (4.5), fatigue (2.9), lethargy (2.8), insomnia (1.2), nervousness (0.8), bizarre dreams (1.0), depression (0.8), impotence (1.2), dyspnea (2.4), pharyngitis (2.0), rhinitis (1.4), upper respiratory infection (2.6), dyspepsia (4.7), nausea (1.6), diarrhea (2.0), chest pain (2.4), arthralgia (3.1), rash (1.2). Betaxolol adverse events reported in European controlled clinical trials: bradycardia (5.8), symptomatic bradycardia (1.9), palpitation (1.9), edema (1.3), cold extremities (1.9), headache (14.8), dizziness (14.8), fatigue (9.7), asthenia (7.1), insomnia (5.0), paresthesia (1.9), nausea (5.8), dyspepsia (3.9), diarrhea (1.9), chest pain (7.1), joint pain (5.2), myalgia (3.2). The following adverse events reported in less than 2% of patients occurred under conditions where a causal relationship is uncertain: flushing, salivation, sweating, allergy, fever, malaise, pain, rigors, angina pectoris, arrhythmia, heart failure, hypertension, hypotension, myocardial infarction, thrombosis, syncope, neuropathy, numbness, speech disorder, stupor, tremor, twitching, anorexia, constipation, dry mouth, increased appetite, mouth ulceration, rectal disorders, vomiting, dysphagia, earache, labyrinth disorders, tinnitus, deafness, leucocytosis, lymphadenopathy, thrombocytopenia, increased AST, increased ALT, acidosis, diabetes, hypercholesterolemia, hyperglycemia, hyperkalemia, hyperlipemia, hyperuricemia, hypokalemia, weight gain, increased LDH, arthropathy, neck pain, muscle cramps, tendonitis, abnormal thinking, amnesia, confusion, emotional lability, hallucinations, decreased libido, breast pain, breast fibroadenosis, menstrual disorder, prostatitis, bronchitis, bronchospasm, cough, epistaxis, flu, pneumonia, sinusitis, pruritus, skin disorders, abnormal taste, taste loss, cystitis, dysuria, proteinuria, abnormal renal function, renal pain, cerebrovascular disorder, leg cramps, peripheral ischemia, thrombophlebitis, abnormal lacrimation, abnormal vision, conjunctivitis, dry eyes, iritis, cataract. Although not reported in clinical studies with betaxolol, a variety of adverse effects have been reported with other beta-adrenergic blocking agents and may be considered potential adverse effects of betaxolol: reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability with slightly clouded sensorium, and decreased performance on neuropsychometric tests, intensification of AV block and congestive heart failure (or cardiac failure), erythematous rash, fever combined with aching and sore throat, laryngospasm, respiratory distress, agranulocytosis, thrombocytopenic purpura, and nonthrombocytopenic purpura, mesenteric arterial thrombosis, ischemic colitis, reversible alopecia, Peyronie's disease, Raynaud's phenomena, skin rashes and/or dry eyes, and oculomucocutaneous syndrome.

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Circadian Rhythmicity of Rate-Normalized QT Interval in Hypothyroidism and Its Significance for Development of Class III Antiarrhythmic Agents

Jonnalagedda S. M. Sarma, PhD, Kalyanasundaram Venkataraman, MD, Pascal Nicod, MD, Ralf Polikar, MD, Johana Smith, RN, Mary P. Schoenbaum, RN, and Bramah N. Singh, MD, PhD

Lengthening of repolarization and refractoriness occurs in hypothyroidism; it is associated with a reduced probability of arrhythmias, with the converse occurring in hyperthyroidism. Because the QT interval and its circadian rhythmicity relative to heart rate is poorly defined in man, we used our new computer-assisted technique to measure QT interval in our analysis of 24-hour Holter tapes before and after (8 to 12 weeks) thyroxine (T_4) replacement in 10 patients with hypothyroidism; the findings were compared to those in 6 normal control subjects. QTc interval was prolonged ($p < 0.02$) and heart rate decreased ($p < 0.005$) during the hypothyroid state. Data were analyzed for circadian rhythmicity by repeated-measures analysis. Circadian variation in QTc and heart rate was statistically significant during hypothyroid and euthyroid states ($p < 0.001$) as well as in control subjects, but the circadian rhythmicity of QTc interval and heart rate were out of phase; the maximum prolongation of QTc occurred between midnight and 6 A.M., at a time when heart rate was at its lowest. QTc interval remained significantly prolonged after 8 to 12 weeks of T_4 replacement, when biochemical indexes of hypothyroidism had returned to normal values. The computer-assisted QTc interval determination technique that we used, and our data on the circadian rhythmicity of QTc and heart rate, have significant implications for the development of new class III antiarrhythmic agents.

(Am J Cardiol 1990;66:959–963)

Since first suggested by Singh and Vaughan Williams[1,2] in 1970, prolongation of cardiac repolarization with corresponding lengthening of ventricular refractoriness has become an increasingly accepted antiarrhythmic mechanism.[3] A variety of interventions that lengthen the QTc interval may also produce either an anti- or proarrhythmic effect, such as torsades de pointes.[4] The circumstances under which prolonged repolarization constitutes either an anti- or proarrhythmic mechanism is thus of clinical relevance.[5] Numerous reports have confirmed that repolarization lengthens in hypothyroidism; the converse occurs in hyperthyroidism.[6–8] These findings are consistent with observations that atrial fibrillation is common in thyrotoxicosis, while most arrhythmias are rare in hypothyroidism. Moreover, despite marked QTc prolongation in hypothyroidism, torsades de pointes is unusual without hypokalemia.[5,9] Hypothyroid cardiac muscle also exhibits electrophysiologic properties similar to those induced by amiodarone,[10] which may exert at least part of its salutary effect on arrhythmias by selectively inhibiting triiodothyronine (T_3) actions in the heart.[2,5,10,11] It thus became of interest to determine the degree of QTc prolongation in hypothyroidism relative to changes in heart rate. Because changes in repolarization are inextricably linked to those in heart rate, a new computer method was developed to help determine the nature of circadian rhythmicity in heart rate and in QT intervals from ambulatory electrocardiographic (Holter) recordings in patients with hypothyroidism before and after thyroid replacement. The changes observed are compared to those found in normal control subjects.

METHODS

Patient population: The study population comprised 10 patients (1 man, 9 women; age 52 ± 12 years) referred to the University of California Medical Center, San Diego, for treatment of primary hypothyroidism. Two patients had a history of cardiac disease and 3 had hypertension. None was taking QT-prolonging drugs or had signs of heart failure. Six people (mean age 56 ± 10) without heart or thyroid disease served as control subjects.

Thyroid function tests: Plasma thyroxine (T_4) and thyroid-stimulating hormone (TSH) levels were measured using standard methods.[12]

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Protocol: Each patient had one 24-hour Holter (Del Mar Avionics, Irvine, California) recording with 2 electrocardiographic leads (equivalent to V_5 and aV_F) before the commencement of T_4 treatment, and a second under euthyroid conditions after 17 ± 8 weeks of therapy. T_4 dosage ranged from 50 to 200 μg/day (mean 118 ± 40 μg/day). Holter recordings for control subjects were obtained once. Patient tapes were analyzed retrospectively, with the operator blinded to the patient's thyroid state. For each patient the same ECG leads were analyzed before and after hormone replacement.

Measurements from the Holter recordings: Holter tapes were replayed at 120 times the recording speed into a Norland 3001 programmable wave form analyzer (Madison, Wisconsin) controlled by a personal computer (IBM-PC/AT) (IBM Personal Computer Division, Boca Raton, Florida) through an IEEE-488 interface (National Instruments, Austin, Texas). The tape player was custom-built, with the frequency response of its analog output amplifiers adjusted to account for the high replay speed. The wave form analyzer was programmed to digitize the input analog signal at a rate of 10 μs/sample and to capture a segment containing 2 or more

TABLE I Mean (± SD) Thyroid Hormone Indexes of the 10 Patients Before and After Thyroxine Therapy

	TSH (μU/ml)	T_4 (μg/dl)
Initial	91 ± 74	2.4 ± 1.9
Treated	2.1 ± 3.5	10.7 ± 4.5
p Value	<0.001	<0.001

SD = standard deviation; TSH = thyroid-stimulating hormone plasma level; T_4 = thyroxine plasma level.

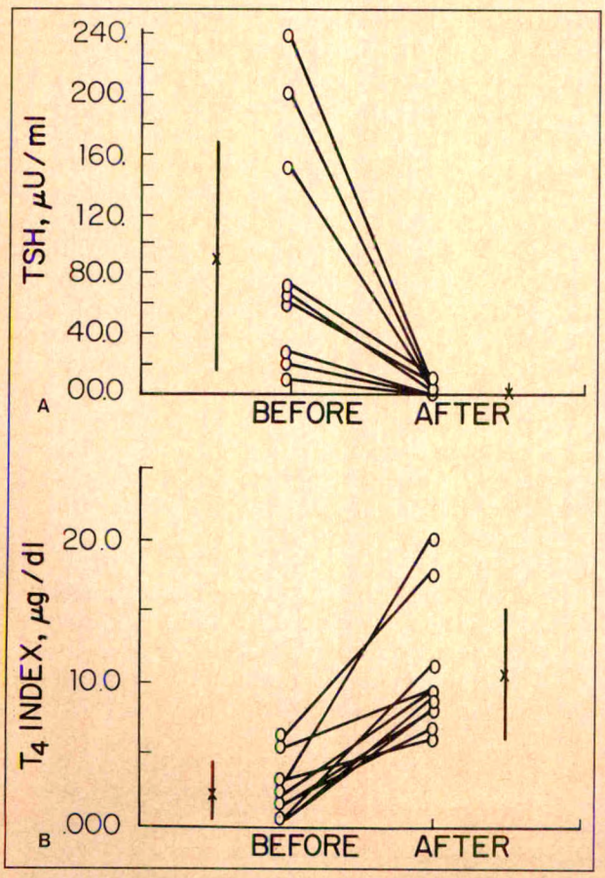


FIGURE 1. Thyroid indexes of individual patients before and after T_4 replacement therapy. TSH = thyroid-stimulating hormone.

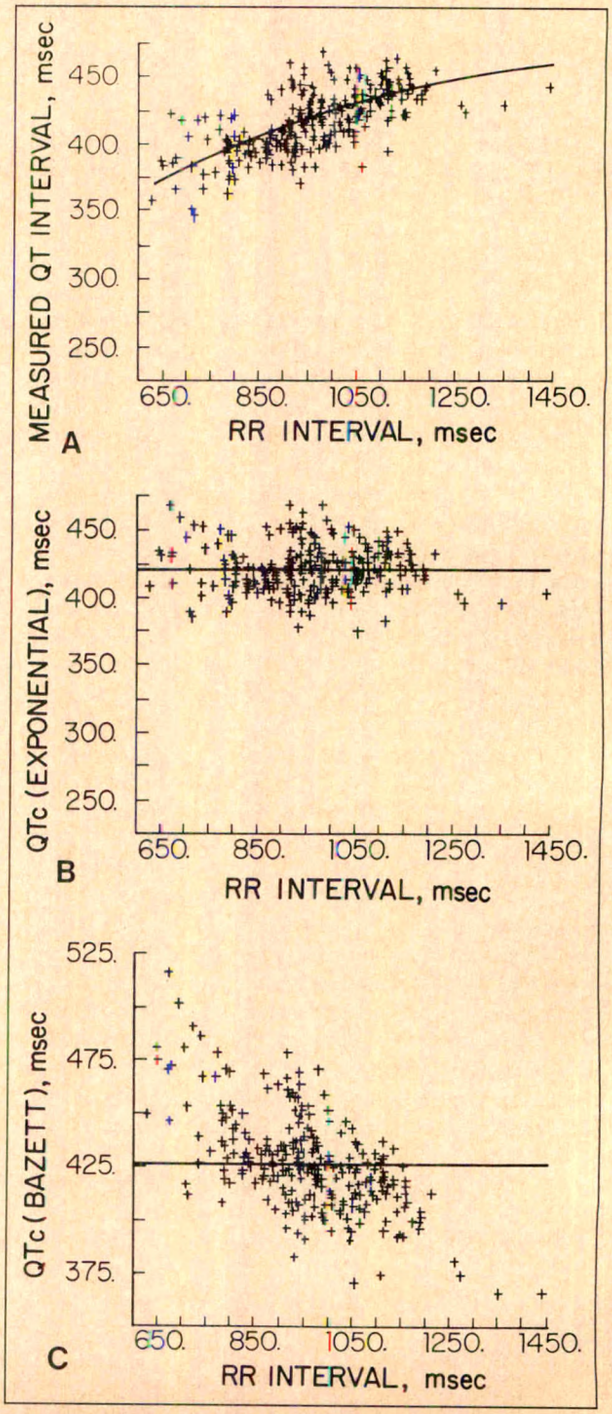


FIGURE 2. Normalization of the QT interval using the exponential formula and comparison with Bazett's QTc, in a typical case. *A*, measured QT intervals plotted against the corresponding cycle length (RR) intervals and fitted by an exponential curve *(solid line)*. *B*, plot of the QTc intervals obtained by the normalization procedure using the exponential formula. *C*, plot of the QTc intervals obtained by Bazett's formula. The X-axis (RR interval) is identical in all 3 panels. *Horizontal solid lines* represent the mean QTc.

QRS complexes on the monitor screen at approximately 5-minute intervals of real time. Cycle length (RR) and QT intervals were then measured in a semi-automated manner under program control. The end of the T wave was identified as the point at which the regression line through the steepest portion of the terminal limb of the T wave intersects the isoelectric line connecting the PQ segments on either side. The method used to determine the QT interval has been validated with respect to accuracy and reproducibility.[13] The measured values were automatically transmitted to a data file in the IBM-PC/AT, which also recorded the time of measurement, later converted to the absolute time of the day of recording. A typical QT-RR measurement took 5 to 7 seconds. The Holter tape was played continuously to preserve the temporal relations among sequential measurements.

Data analysis: Observed QT values were normalized[13] for RR as follows. First, the QT-RR data were fit to the exponential formula $QT = A - B \cdot \exp(-k \cdot RR)$ by a nonlinear regression analysis using ASYST scientific software (ASYST Software Technologies, Rochester, New York). The normalized QT interval (QTc) was defined as the estimated value of the measured QT interval at RR = 1000 ms, which leads to the formula $QTc = QT - B[\exp(-k \cdot 1000) - \exp(-k \cdot RR)]$, where QTc, QT, and RR are expressed in milliseconds.

The normalized QT intervals were averaged over 3-hour periods and plotted against the time of the day of recording. To get a midnight to midnight representation of QTc in each patient, the data after the 0 hour of the second day were wrapped around to the 0 hour of the first day.

Statistical analysis: The QTc and heart rate changes caused by the time of the day were evaluated by analysis of variance with repeated measures, using thyroid condition (hypothyroid versus euthyroid) as the grouping factor. The differences among the control, hypothyroid and euthyroid groups were evaluated by the analysis of variance methods. The BMDP2V program (BMDP Statistical Software, Los Angeles, California) was used. Thyroid indexes before and after treatment were evaluated by paired *t* tests.

RESULTS

The thyroid indexes (TSH and T_4) of each patient before and after therapy are shown in Figure 1 and the mean values listed in Table I.

A typical QT-RR plot with the exponential regression line is shown in Figure 2A. The QT intervals from Figure 2A were normalized to RR = 1000 ms and plotted against the RR along with the horizontal line representing the estimated mean value of QT at RR = 1000 ms in Figure 2B. The individual data points in Figure 2B are randomly distributed around the line parallel to the RR axis, showing that the overall dependence of QT interval on the cycle length has been removed by the normalization process. For comparison, the QT intervals shown in Figure 2A were also normalized using Bazett's formula and plotted against the RR along with the horizontal line representing the mean QTc (Bazett) in Figure 2C. The data points formed a nonrandom pattern, and the QTc was overestimated at higher and underestimated at. lower heart rates, implying that Bazett's formula was not adequate for QT interval normalization in this case. Bazett's formula appeared adequate only when the RR intervals did not vary too much from 1000 milliseconds.

The QTc and heart rate values averaged over a 3-hour period plotted against the time of day are shown in Figure 3. Circadian variation in QTc and heart rate was statistically significant according to the repeated-measures analysis in all groups studied ($p < 0.001$). The circadian rhythmicities of QTc and heart rate are qualitatively similar among the 3 groups. The QTc was prolonged ($p < 0.02$) and the heart rate decreased ($p < 0.005$) during the hypothyroid compared to the euthyroid state according to a 2-way analysis of variance in which the time of day and thyroid condition were specified as cofactors. However, as seen in Figure 3, the QTc remained significantly prolonged in the euthyroid state attained after T_4 treatment compared to the control group ($p < 0.001$). The circadian variability in the control group QTc appears more pronounced between midnight and 6 A.M. than in the other 2 groups. In contrast

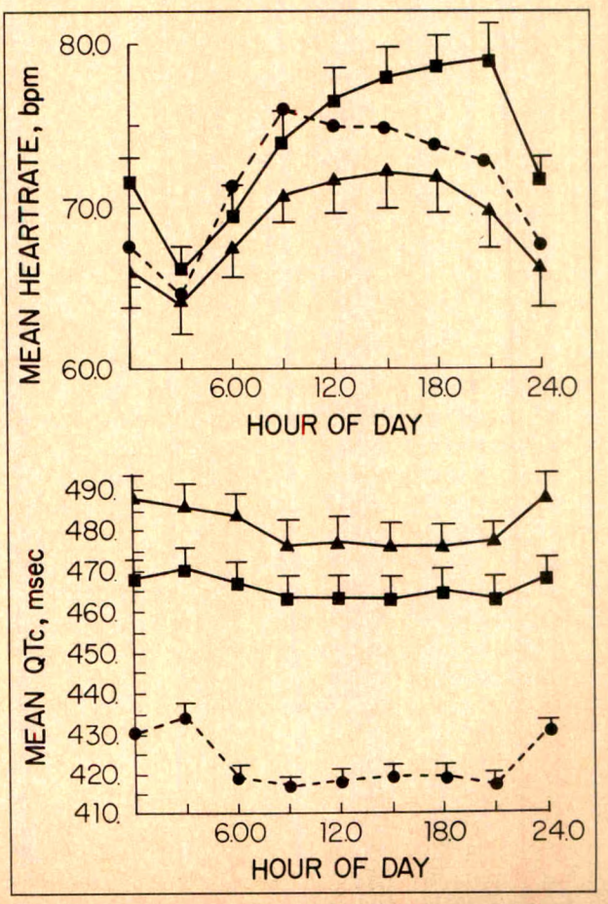


FIGURE 3. Circadian variation of the mean values of heart rate and QTc in hypothyroid *(triangles)*, euthyroid *(squares)* and control *(circles)* groups. Error bars (not plotted for control heart rates) represent standard error of the mean. Data for hypothyroids and euthyroids are from the same patients before and after thyroid hormone replacements; data for control subjects are from 6 normal euthyroid people in a similar age group.

TABLE II Mean Values of Heart Rate and QTc Over Six-Hour Segments of the Day

Hour of the Day	Thyroid State	HR ± SEM (min/max)* (beats/min)	QTc ± SEM (min/max)* (ms)
0	Hypothyroid	67 ± 4 (54/88)	487 ± 12 (432/579)
	Euthyroid	72 ± 3 (60/94)	467 ± 9 (406/520)
	Control	68 ± 2 (55/90)	430 ± 6 (389/484)
6	Hypothyroid	69 ± 4 (54/95)	481 ± 12 (417/569)
	Euthyroid	72 ± 4 (55/107)	467 ± 10 (395/540)
	Control	74 ± 3 (52/106)	421 ± 5 (368/483)
12	Hypothyroid	73 ± 4 (54/98)	476 ± 12 (409/573)
	Euthyroid	78 ± 4 (57/106)	464 ± 10 (395/539)
	Control	77 ± 4 (56/113)	418 ± 6 (374/482)
18	Hypothyroid	74 ± 4 (57/97)	474 ± 11 (415/548)
	Euthyroid	80 ± 4 (62/98)	465 ± 11 (426/515)
	Control	76 ± 4 (58/102)	420 ± 6 (381/468)

* Average minimum (Min) and maximum (Max) values in the specified time periods.
Data for hypothyroids and euthyroids are from the same patients before and after thyroid hormone replacements; data for control subjects are from 6 normal euthyroid people.
HR = heart rate; SEM = standard error of the mean.

the obvious differences in QTc between the control and thyroid patient groups, the heart rates of control subjects were not significantly different from the heart rates of either the hypothyroid or euthyroid groups, although certain trends are apparent: the mean heart rates of the hypothyroid group are the lowest throughout the day; between noon and midnight, the heart rates of the euthyroid group are the highest, followed by those of control and hypothyroid groups.

Table II lists the mean values of heart rate and QTc over 6-hour segments of the day. The average minimum and maximum values in the specified time period are also presented. The heart rate was lower and QTc longer between midnight and early morning in all groups studied.

DISCUSSION

Circadian rhythmicity of QTc and thyroid hormone effects: In recent years, numerous studies have demonstrated a circadian periodicity in the occurrence of a large number of cardiovascular disorders,[14] including the frequency of myocardial infarction,[15] silent and symptomatic ischemia,[16] sudden death[17] and strokes.[18] Our data have indicated a distinct circadian rhythmicity in the case of the QTc interval in normal subjects as well as in patients with hypothyroidism. In the latter, the pattern persisted, albeit in a somewhat attenuated form, after biochemical euthyroidism was attained. Although the direct effect of heart rate on the QT interval had been eliminated by the normalization process, the QTc circadian rhythm was clearly in opposite phase to that of the heart rate. Such an inverse relation indicates opposing net effects of the autonomic nervous system on these parameters. The circadian periodicity of heart rate in man correlates closely with that in plasma catecholamine levels.[19] Over 24 hours, however, the relative effects of the sympathetic and parasympathetic transmitters on the ventricular myocardium are not clearly defined. In normal subjects, Browne et al[20,21] showed that the QT interval is prolonged during sleep, independent of accompanying bradycardia. They attribute this to changes in autonomic tone occurring during sleep. Bexton et al[22] studied the circadian variation of QTc (corrected for rate by the Bazett formula) in groups of patients with varying degrees of cardiac denervation and confirmed the presence of circadian rhythm in normally innervated hearts. Their results suggest that the circadian rhythm of QTc depends on neurally mediated autonomic tone and the circadian variation of circulating catecholamines. Alexopoulos et al,[23] assuming a linear QT-RR relationship, reached similar conclusions based on their studies in cardiac transplanted patients.

Hypothyroidism as a potential class III antiarrhythmic action: Our data establish that the QTc interval in hypothyroidism is significantly prolonged over 24 hours. The fact that it is longest between midnight and 6 AM, when the vagal tone is highest and the sympathetic tone lowest, may be of clinical importance. That the QTc lengthens to its greatest extent during sleep is consistent with the longest refractory period in the heart over the same time period. It is tempting to speculate that this accounts for the lowest incidence of sudden death during this time period compared to other segments of time during a 24-hour period.[21] In the BHAT trial, an analysis of the circadian rhythmicity of sudden death again revealed the lowest incidence to be between midnight and 6 AM during chronic beta-blocking therapy in the survivors of acute myocardial infarction.[24] In the case of hypothyroidism, the QTc lengthening over the entire 24-hour period raises the issue of whether the corresponding prolongation of the refractory period may constitute a sustained continuous antifibrillatory mechanism. This is consistent with the clinical observations that ventricular arrhythmias and sudden death are uncommon in hypothyroidism.[5] Particularly noteworthy is that torsades de pointes is known to be uncommon, despite the marked lengthening of the QTc interval and bradycardia. This is strikingly similar to the effects of chronic amiodarone administration, which exerts an unusually potent action on a variety of tachyarrhythmias.[10] Indeed, there is increasing evidence that the fundamental mechanism of amiodarone may stem from a cardioselective inhibition of T_3 myocardial nuclear receptor.[5,10,11] Our data on the time course of regression of prolonged QTc interval in hypothyroidism after hormone replacement, although unexpected, is therefore of major importance. The complete restoration of the biochemical indexes of thyroid function by T_4 replacement over 8 to 12 weeks did not, for example, normalize the QTc interval but did eliminate the bradycardic effect of hypothyroidism. Further observations during a longer follow-up period will be of interest. Our findings suggest that the myocardial membrane effects of thyroid hormones are dissociated from serum biochemical indexes. It is possible that the alterations in membrane proteins induced by hypothyroidism have longer half-lives, outlasting the time it takes for a return to biochemical euthyroidism.[27] Such a parallelism exists in the case of the onset and offset of antiarrhythmic actions and plas-

ma drug levels of amiodarone in man. In neither instance are there electrophysiologic mechanisms that account for these observations. Polikar et al,[25] who studied a larger subset of our population of hypothyroid patients, found that T_4 replacement did not significantly increase the frequency of ventricular premature beats or produce new ventricular arrhythmias, but these patients were not preselected on the basis of their arrhythmias. While the precise nature of the delayed resolution of prolonged QTc interval after thyroid replacement in hypothyroids remains uncertain, the electrophysiologic consequence of such a longtime course is clearly of major importance in the control of life-threatening cardiac arrhythmias by agents that produce selective T_3 inhibition in the heart.

Clinical implications: The methodology used in this study to measure and analyze QT intervals is novel and theoretically more sensitive than previous methods because the nonlinear nature of the QT-RR relation is taken into consideration. The computer-aided electronic measurement of QT intervals is about an order of magnitude more accurate than those from paper traces. An obvious application of the present methodology is the monitoring of antiarrhythmic therapy, especially with the expanding range of newer agents that act by prolonging cardiac repolarization.[3,5] A careful analysis of the variation of rate-normalized QT interval over a 24-hour period, rather than measurements made at isolated times, may provide further insights regarding the beneficial versus deleterious effects of prolonged cardiac repolarization during the pharmacologic control of arrhythmias.

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Chronic Transvenous Pacemaker Lead Removal Using a Unique, Sequential Transvenous System

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Transvenous removal of 43 consecutive chronic pacemaker leads was successful in 28 patients. For leads not removed by traction at the pacemaker connection terminal, a unique locking stylet was advanced through the inner coil lumen and engaged at the tip to allow traction without lead elongation. Leads not extracted with the locking stylet alone had traction maintained on the stylet as sheaths were advanced over the lead to dilate and detach any fibrous tissue adherent to the lead. By applying traction at the pacemaker connection terminal, 2 leads were removed. The locking stylet alone extracted 9 leads. Both the locking stylet and sheaths were necessary to explant 32 leads. There were 15 right atrial and 22 right ventricular leads completely removed. Additionally, 6 right ventricular leads were subtotally removed leaving only the tip in the right ventricular apex. Avulsed myocardium was removed with the lead in 1 patient without sequelae. A subacute hemothorax developed in 1 patient 18 days after discharge requiring drainage, and subclavian vein thrombosis developed in another, which was successfully treated with anticoagulation. Hypotension occurred in 1 patient during final positioning of new leads, which responded to conservative treatment. Chronic pacemaker leads can be reliably removed without thoracotomy. Both a unique locking stylet to allow traction without lead elongation and a sheath to dilate and detach adherent fibrous tissue are needed for consistent success. Recognized complications included myocardial avulsion without sequelae, subacute hemothorax, subclavian vein thrombosis and transient hypotension.

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Transvenous endocardial pacemaker lead design has stressed biocompatibility, corrosion resistance, durability, flexibility and permanent endocardial fixation. Lead removal, or exchange, has not been considered an important design issue. Although nonfunctional foreign material is generally removed from the body, chronic transvenous endocardial pacemaker leads are removed only if they become infected, threatening the patient's survival, or if they pose an anatomic obstacle.[1] This practice has been adopted as a compromise to avoid a thoracotomy which was often required to remove such leads.[2,3] Removal by manual traction is difficult and provides inconsistent results because permanent transvenous leads develop focal fibrous adhesions along their course.[4] In the future, it will become increasingly important to free the venous system of this excess, nonfunctional material to avoid complications of retained transvenous leads and allow placement and proper function of new systems. We report the early results of chronic transvenous pacemaker lead removal using a unique, sequential system (Cook Pacemakers, Inc., Leechburg, Pennsylvania) that does not require a thoracotomy and provides consistent results.

METHODS

After sterile preparation, draping and adequate anesthesia, the pacemaker pocket is opened and the pulse generator is explanted. The lead to be removed is then carefully exposed to the lead insertion site at the central vein, avoiding damage to either the insulation or the conductor coil. A special pair of sharp wire cutters permits exposure of the conductor coil without crushing the conductor coil lumen. A standard 60-cm stylet is advanced through the conductor coil to the lead tip clearing the lead of any debris. A conical, steel lead-expander is used to dilate the tip of the conductor coil facilitating appropriate sizing of the conductor coil lumen. Gauge pins, calibrated in thousandths of an inch diameter, are used to measure the conductor coil lumen diameter. Grasping the lead with a Silastic-tipped hemostat permits control of the insulation and conductor coil during cutting, dilating and gauging. The locking stylet, constructed in sizes analogous to the gauge pins, is composed of a relatively stiff, 60-cm wire with a fine wire wound clockwise and braised to its tip (Figure 1). The appropriate gauge-locking stylet is advanced through the conductor coil lumen to the lead tip and rotated counterclockwise 10 to 15 times. Gentle pulling on the locking stylet assures engagement. Once engaged, pulling the locking stylet results in traction at the lead tip without lead elongation (Figure 2). A strong suture is

tied around the insulation of the lead at its most proximal portion. The suture is then brought to the proximal end of the locking stylet and tied to the loop. If gentle traction fails to remove the lead, the telescoping Byrd dilators are passed over the locking stylet/lead assembly to the insertion site of the vein. A special pin-vice is firmly attached to the proximal end of the inner Byrd dilator (Figure 3). Continuous traction on the locking stylet and firm rotation and advancement of the smaller dilator permits entry into the vascular space. The larger dilator is then telescoped over the smaller dilator into the vascular space. Sequentially, under fluoroscopic control, both dilators are passed through the vascular space, over the pacemaker lead, dilating and detaching any fibrous adhesions. Frequently in this process, a critical fibrotic adhesion is removed and the lead is abruptly disengaged. If this does not occur, the dilators are advanced to the lead/myocardium interface and moderate, continuous traction can be placed at the lead tip with the locking stylet, while the larger dilator is used to prevent invagination of the right ventricular wall. After the lead is disengaged, it is pulled inside the dilator allowing the lead, locking stylet and dilator to be removed together. Firm pressure is then held at the insertion site to the vein until hemostasis is assured. All instruments used in lead extractions were developed in conjunction with Cook Pacemaker Corporation, Leechburg, Pennsylvania.

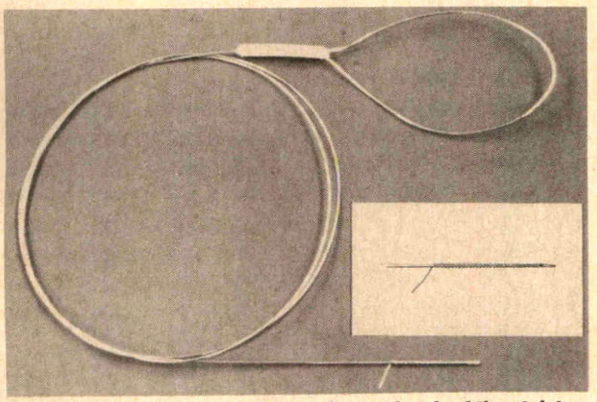


FIGURE 1. Locking stylet. Insert shows sketch of the stylet distal tip.

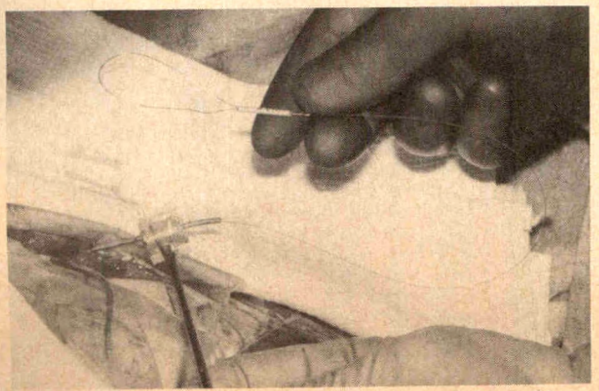


FIGURE 2. Locking stylet in place through conductor coil lumen.

RESULTS

Patients who were having permanent pacemaker leads removed between December 19, 1988, and January 22, 1990, at The Cleveland Clinic Foundation, Cleveland, Ohio, were considered candidates for use of this system. Data collected included patient age and gender, number of leads removed, approach used, primary indication for lead removal, lead characteristics, removal instruments used and complications. Leads in place a minimum of 4 months were included. Leads that had been cut and were too short to attempt removal with the locking stylet were excluded.

Mean age in these 28 patients (16 men and 12 women) was 61 years (range 35 to 82). Forty-three consecutive leads implanted 4 to 174 months were successfully removed. The leads had been inserted by several techniques. Venous approaches used included 22 left subclavian, 15 right subclavian, 2 right cephalic, 3 left cephalic and 1 left external jugular. Primary indications for lead removal included infection (1 patient), septicemia or endocarditis (1 patient), prophylaxis or replacement (25 patients) and pain (1 patient). Unipolar leads numbered 31; 11 were bipolar, 1 was tripolar, 10 were silicone and 33 were polyurethane coated. Lead fixation mechanisms included 32 passive systems (tine, fins, flange) and 11 active systems (screw, hook). By applying traction at the pacemaker connection terminal 2 leads were removed. The locking stylet alone was used to extract 9 leads. Both the locking stylet and sheaths were necessary to explant 32 leads. Leads removed with this system often have dense fibrous tissue attached (Figure 4). Fifteen right atrial (100%) and 22 right ventricular (79%) leads (mean in vivo time 57 months) were completely removed; 6 right ventricular (21%) leads (mean in vivo time 90 months) were subtotally

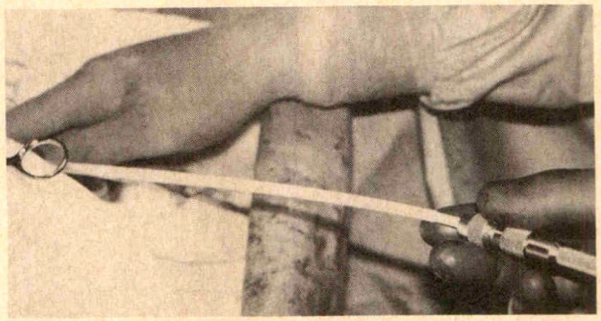


FIGURE 3. Pin-vice attached to the inner Byrd dilator is rotated and advanced over the locking stylet/lead assembly.

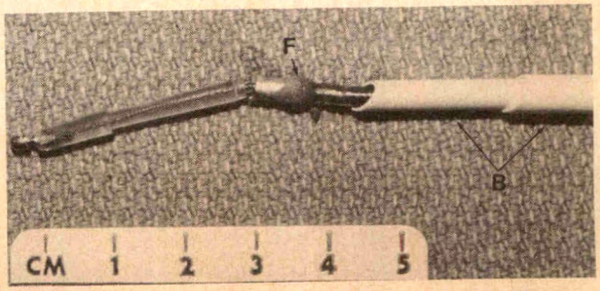


FIGURE 4. Explanted chronic lead showing adherent fibrous tissue and telescoping Byrd dilators.

removed, leaving only the tip in the right ventricular apex. The mean in vivo time was not statistically different ($p < 0.14$) between the ventricular leads completely extracted and the ventricular leads incompletely extracted using Student's t test (2-tailed). By the Fischer's exact test, the probability of completely extracting leads was not affected by the duration of time implanted ($p = 0.14$).

Complications occurred in 4 patients involving a total of 6 explanted leads. A myocardial avulsion occurred in 1 patients without sequelae. Eighteen days after discharge, a subacute hemothorax developed in 1 patient which required drainage; in this patient, 2 transvenous leads that had been implanted at the time of lead removal were left in situ. Another patient developed a subclavian vein thrombosis which was successfully treated with anticoagulation; the transvenous lead that had been implanted at the time of lead removal was left in situ. In 1 patient, hypotension, thought to be related to sedation, developed 30 minutes after lead explantation during the positioning of the new lead. Conservative therapy resulted in blood pressure normalization.

DISCUSSION

This lead extraction system has been consistently successful without adverse sequelae in elderly patients. Lead removal was successful in all 43 attempts. Lead implantation approach, insulation type, polarity or fixation mechanism has not interfered with explantation using this technique. The majority of leads removed were sterile, supernumerary or nonfunctional leads. In most cases, both a locking stylet and sheaths were necessary to remove the lead. This is expected as the locking stylet is designed to provide traction. The addition of the sheaths allows disruption of the focal fibrous adhesions along the course of the lead and traction at the distal tip without invagination of the right ventricular wall when the sheaths are advanced to the myocardium.

Incomplete extraction occurred in cases when the locking stylet was undersized and engaged proximal to the lead tip resulting in lead elongation and breakage distal to the locking stylet. This is related to difficulty in choosing the locking stylet of the appropriate gauge. Incorrect gauging may be due to previous traction at the pacemaker connection terminal which can elongate the lead and deform conductor coil lumen. Subsequently, passage of the locking stylet to the lead tip can be difficult. This has never resulted in failure to remove a lead using this system.

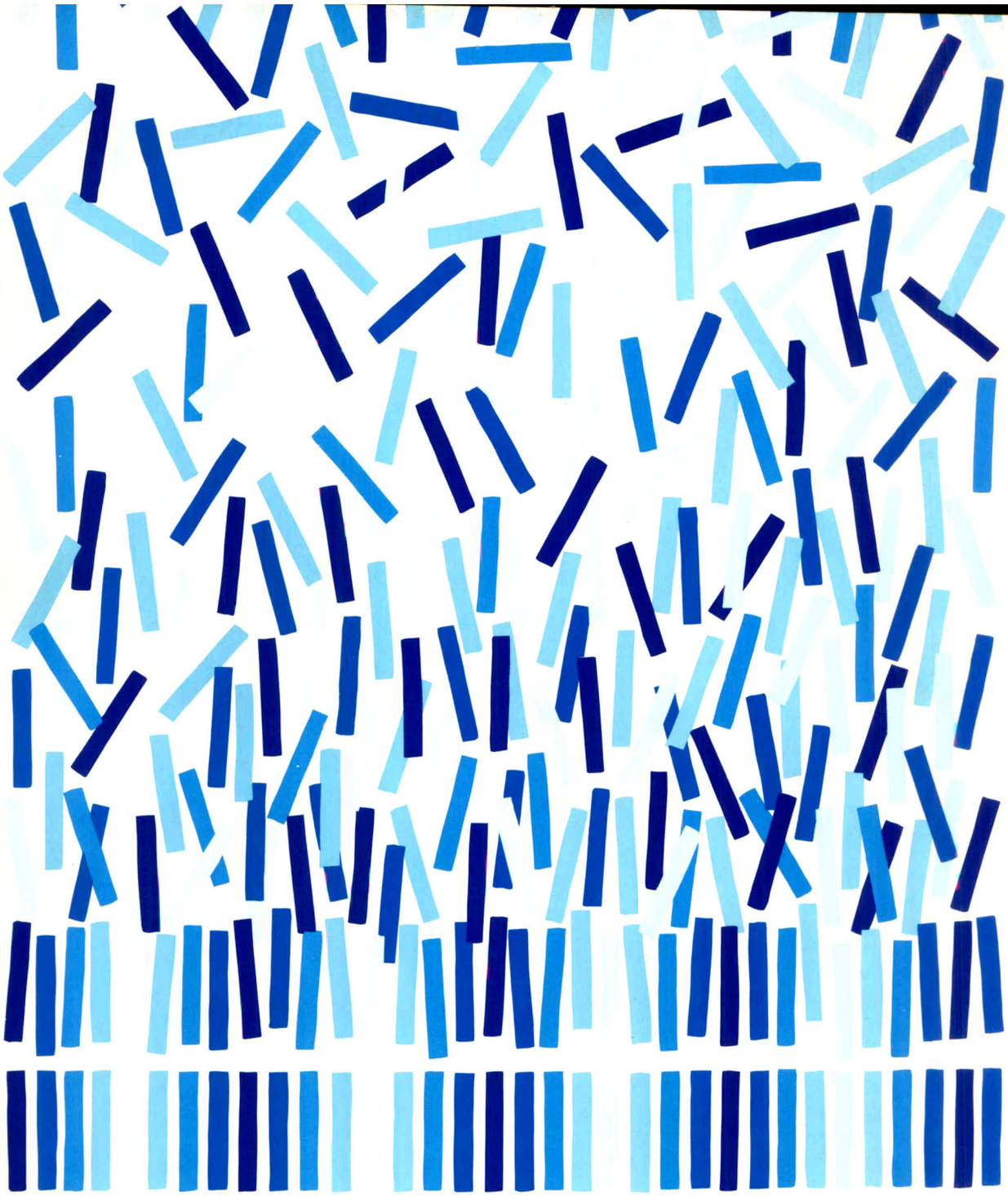
The case in which a myocardial avulsion occurred involved a polyurethane insulated lead where the fibrous tissue had grown under the insulation at the junction of the insulation and distal electrode. Another patient was noted to have a subacute hemothorax 18 days after hospital discharge. This complication was probably related to lead removal, but could have occurred at the time of lead reinsertion after lead extraction. The case of subclavian thrombosis might have been related to lead extraction, but more likely occurred in relation to lead reinsertion. The hypotension that occurred in 1 patient near the end of pacemaker lead reinsertion was temporally related to a dose of intravenous benzodiazepam. All of the observed complications were successfully treated by conservative methods. Because of the small sample size, firm conclusions regarding complications from the procedure cannot be made.

Permanent transvenous pacemaker lead design has not incorporated a method for easy lead removal. Complications of retained transvenous pacemaker leads include infection, lead migration or embolization and major venous thrombosis.[5–10] Historically, transvenous leads could be removed by traction at the pacemaker connection terminal.[11] Complications associated with forceful and prolonged traction include invagination of the right ventricular wall to the tricuspid valve accompanied by shock, ventricular arrhythmias and lethal hemopericardium.[5] Surgical removal has not been widely practiced for sterile nonfunctional leads as the risks of thoracotomy have been felt to outweigh the risks of leaving the lead in situ.[2] In this article, we have presented the results of a method to explant chronic transvenous pacemaker leads without a thoracotomy that provides consistent lead removal and few complications. This method of lead removal is unique and continues to evolve. The method section describes refinements made in both technique and instruments. Further changes are not likely to alter the basic technique. Despite the apparent safety of this technique, surgical backup is necessary since life-threatening complications could occur. Further studies are necessary to define fully the incidence and spectrum of complications related to this system.

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References: 1. Singh BN, et al. *American Heart J* 116 (5): 1542-1551, 1988. 2. Haffajee CI, et al. *Circ.* 80 (4): II-652, 1989. 3. Valero de Pesce FM, et al. *Z. Electro* 2 (3): 215-221, 1988. 4. Duggerpion TH, et al. JACC 9 (2): 244A, 1987. 5. Ruskin JN, et al. *Circ.* 80 (4): II-652, 1989.

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Most Common Adverse Events	Percent of Incidence	Percent Who Discontinued
Dizziness	12.5	2.4
Nausea/Vomiting	10.7	3.4
Unusual Taste	8.8	0.7
Constipation	7.2	0.5
Fatigue	6.0	1.0
Most Serious Adverse Events		
Proarrhythmia	4.7	
Congestive Heart Failure	3.7	
Third Degree AV Block	0.2	

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Patient selection

Indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that in the judgment of the physician, are life-threatening. There is no evidence from controlled trials that the use of any antiarrhythmic agent favorably affects survival or the incidence of sudden death. Therefore the use of Rythmol should be reserved for patients whom in the opinion of the physician the benefits of treatment outweigh the risks.

Rythmol and the CAST results

Although Rythmol was not included in CAST, the applicability of the Cardiac Arrhythmia Suppression Trial results to other populations (e.g., those without recent myocardial infarction), to Rythmol, or to other antiarrhythmic drugs is uncertain, but at present it is prudent to consider any 1C agent, such as Rythmol to have a similar risk.

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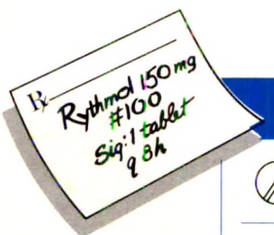
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RYTHMOL (propafenone HCl) is indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that in the judgement of the physician, are life threatening. Because of the proarrhythmic effects of RYTHMOL, its use should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks. The use of RYTHMOL is not recommended for use in patients with less severe ventricular arrhythmias, even if the patients are symptomatic. Use of RYTHMOL for the treatment of sustained ventricular tachycardia, like other antiarrhythmics, should be initiated in the hospital.

CONTRAINDICATIONS

RYTHMOL (propafenone HCl) is contraindicated in the presence of uncontrolled congestive heart failure, cardiogenic shock, sinoatrial, atrioventricular and intraventricular disorders of impulse generation and/or conduction (e.g., sick sinus node syndrome, atrioventricular block) in the absence of an artificial pacemaker, bradycardia, marked hypotension, bronchospastic disorders, manifest electrolyte imbalance, and known hypersensitivity to the drug.

WARNINGS:

Mortality: In the National Heart Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a longterm, multicenter, randomized, double blind study in patients with asymptomatic non life threatening ventricular ectopy who had a myocardial infarction more than six days but less than two years previously and demonstrated mild to moderate left ventricular dysfunction, an excessive mortality or nonfatal cardiac arrest rate was seen in patients treated with encainide or flecainide (56/730) compared with that seen in patients assigned to carefully matched placebo treated groups (22/725). The average duration of treatment with encainide or flecainide in this study was ten months.The applicability of these results to other populations (e.g., those without recent myocardial infarction and to other antiarrhythmic drugs) is uncertain, but at present it is prudent (1) to consider any IC agent (especially one documented to provoke new serious arrhythmias) to have a similar risk and (2) to consider the risks of Class IC agents, coupled with the lack of any evidence of improved survival, generally unacceptable in patients without life threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life threatening, symptoms or signs.

Proarrhythmic Effects

RYTHMOL, like other antiarrhythmic agents, may cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia, ventricular fibrillation or torsade de pointes; i.e., tachycardia that is more sustained or more rapid which may lead to fatal consequences. It is therefore essential that each patient given RYTHMOL be evaluated electrocardiographically and clinically prior to, and during therapy to determine whether the response to RYTHMOL (propafenone HCl) supports continued treatment.Overall in clinical trials with propafenone, 4.7% of all patients had new or worsened ventricular arrhythmia possibly representing a proarrhythmic event (0.7% was an increase in PVCs; 4.0% a worsening, or new appearance, of VT or VF). Of the patients who had a worsening of VT (4%), 92% had a history of VT and/or VT/VF, 71% had coronary artery disease, and 68% had a prior myocardial infarction. The incidence of proarrhythmia in patients with less serious or benign arrhythmias, which include patients with an increase in frequency of PVCs, was 1.6%. Although most proarrhythmic events occurred during the first week of therapy, late events also were seen and the CAST study (see above) suggests that an increased risk is present throughout treatment.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)

PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE PROPAFENONE or other agents with beta adrenergic blocking activity.

Congestive Heart Failure

During treatment with oral propafenone in patients with depressed baseline function (mean EF=33.5%), no significant decreases in ejection fraction were seen. In clinical trial experience, new or worsened CHF has been reported in 3.7% of patients; of those 0.9% were considered probably or definitely related to RYTHMOL. Of the patients with congestive heart failure probably related to propafenone, 80% had preexisting heart failure and 85% had coronary artery disease. CHF attributable to RYTHMOL developed rarely (<0.2%) in patients who had no previous history of CHF. As RYTHMOL exerts both beta blockade and a (dose related) negative inotropic effect on cardiac muscle, patients with congestive heart failure should be fully compensated before receiving RYTHMOL. If congestive heart failure worsens, RYTHMOL should be discontinued (unless congestive heart failure is due to the cardiac arrhythmia) and, if indicated, restarted at a lower dosage only after adequate cardiac compensation has been established.

Conduction Disturbances

RYTHMOL slows atrioventricular conduction and also causes first degree AV block. Average PR interval prolongation and increases in QRS duration are closely correlated with dosage increases and concomitant increases in propafenone plasma concentrations. The incidence of first degree, second degree, and third degree AV block observed in 2,127 patients was 2.5%, 0.6%, and 0.2%, respectively. Development of second or third degree AV block requires a reduction in dosage or discontinuation of RYTHMOL. Bundle branch block (1.2%) and intraventricular conduction delay (1.1%) have been reported in patients receiving propafenone. Bradycardia has also been reported (1.5%). Experience in patients with sick sinus node syndrome is limited and these patients should not be treated with propafenone.

Effects on Pacemaker Threshold

RYTHMOL may alter both pacing and sensing thresholds of artificial pacemakers. Pacemakers should be monitored and programmed accordingly during therapy.

Hematologic Disturbances

One case of agranulocytosis with fever and sepsis, probably related to use of propafenone, was seen in U.S. clinical trials. The agranulocytosis appeared after 8 weeks of therapy. Propafenone therapy was stopped and the white count had normalized by 14 days. The patient recovered. In the course of over 800,000 patient years of exposure during marketing outside the U.S. since 1978, seven additional cases have been reported. In one of these, concomitant captopril, a drug known to cause agranulocytosis, was used. Unexplained fever and/or decrease in white cell count, particularly during the first three months of therapy, warrant consideration of possible agranulocytosis/granulocytopenia. Patients should be instructed to promptly report the development of any signs of infection such as fever, sore throat, or chills.

PRECAUTIONS

Hepatic Dysfunction:

Propafenone is highly metabolized by the liver and should, therefore, be administered cautiously to patients with impaired hepatic function. The dose of propafenone given to patients with impaired hepatic function should be significantly reduced. Careful monitoring for excessive pharmacological effects (see OVERDOSAGE) should be carried out.

Renal Dysfunction:

A considerable percentage of propafenone metabolites (18.5%-38% of the dose/48 hours) are excreted in the urine. Until further data are available, RYTHMOL should be administered cautiously to patients with impaired renal function. These patients should be carefully monitored for signs of overdosage (see OVERDOSAGE).

Elevated ANA Titers:

Positive ANA titers have been reported in patients receiving propafenone. Patients who develop an abnormal ANA test should be carefully evaluated and, if persistent or worsening elevation of ANA titers is detected, consideration should be given to discontinuing therapy.

Impaired Spermatogenesis:

Reversible disorders of spermatogenesis have been demonstrated in monkeys, dogs and rabbits after high dose intravenous administration. Evaluation of the effects of short term propafenone administration on spermatogenesis in 11 normal subjects suggests that propafenone produced a reversible, short term drop (within normal range) in sperm count. Subsequent evaluations in 11 patients receiving propafenone chronically have suggested no effect of propafenone on sperm count.

Drug Interactions: Quinidine: Small doses of quinidine completely inhibit the hydroxylation metabolic pathway, making all patients, in effect, slow metabolizers. There is, as yet, too little information to recommend concomitant use of propafenone and quinidine. **Local Anesthetics:** Concomitant use of local anesthetics may increase the risks of central nervous system side effects. **Digitalis:** RYTHMOL produces dose related increases in serum digoxin levels ranging from about 35% at 450 mg/day to 85% at 900 mg/day propafenone without affecting digoxin renal clearance. Digoxin dosage should ordinarily be reduced when propafenone is started. **Beta-Antagonists:** Propafenone appears to inhibit the hydroxylation pathway for propranolol and metoprolol (just as quinidine inhibits propafenone metabolism). While the therapeutic range for beta-blockers is wide, a reduction in dosage may be necessary during concomitant administration with propafenone. **Warfarin:** In a study of eight healthy subjects receiving propafenone and warfarin concomitantly, mean steady-state warfarin plasma concentrations increased 39% with a corresponding increase in prothrombin times of approximately 25%. It is therefore recommended that prothrombin times be routinely monitored and the dose of warfarin be adjusted if necessary. **Cimetidine:** Concomitant administration of propafenone and cimetidine in 12 healthy subjects resulted in a 20% increase in steady-state plasma concentrations of propafenone with no detectable changes in electrocardiographic parameters beyond that measured on propafenone alone. **Other:** Limited experience with propafenone combined with calcium antagonists and diuretics has been reported without evidence of clinically significant adverse reactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Life time maximally tolerated oral dose studies in mice (up to 360 mg/kg/day) and rats (up to 270 mg/kg/day) provided no evidence of a carcinogenic potential for propafenone. RYTHMOL was not mutagenic when assayed for genotoxicity. **Pregnancy Teratogenic Effects:** Pregnancy Category C.: Propafenone has been shown to be embryotoxic in rabbits and rats when given in doses 10 and 40 times, respectively, the maximum recommended human dose. No teratogenic potential was apparent in either species. There are no adequate and well controlled studies in pregnant women. Propafenone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Pregnancy Nonteratogenic Effects:** In a perinatal and postnatal study in rats, propafenone, at dose levels of 6 or more times the maximum recommended human dose, produced dose dependent increases in maternal and neonatal mortality, decreased maternal and pup body weight gain and reduced neonatal physiological development. **Labor and Delivery:** It is not known whether the use of propafenone during labor or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labor or increases the need for forceps delivery or other obstetrical intervention. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from RYTHMOL, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and efficacy of RYTHMOL in children has not been established.

Geriatric Use: There do not appear to be any age-related differences in adverse reaction rates in the most commonly reported adverse reactions. Because of the possible increased risk of impaired hepatic or renal function in this age group, RYTHMOL should be used with caution. The effective dose may be lower in these patients.

ADVERSE REACTIONS

Adverse reactions associated with RYTHMOL (propafenone HCl) occur most frequently in the gastrointestinal, cardiovascular, and central nervous systems. About 20% of patients discontinued due to adverse reactions.

Adverse reactions reported for ≥1% of 2,127 patients who received propafenone in U.S. clinical trials are presented in the following list. Dizziness, Nausea and/or Vomiting, Unusual Taste, Constipation, Fatigue, Dyspnea, Proarrhythmia, Angina, Headache(s), Blurred Vision, CHF, Ventricular Tachycardia, Dyspepsia, Palpitations, Rash, First Degree AV Block, Diarrhea, Weakness, Dry Mouth, Syncope/Near Syncope, Increased QRS Duration, Chest Pain, Anorexia, Abdominal Pain/Cramps, Ataxia, Insomnia, Premature Ventricular Contraction(s), Bradycardia, Anxiety, Edema, Tremor(s), Diaphoresis, Bundle Branch Block, Drowsiness, Atrial Fibrillation, Flatulence, Hypotension, Intraventricular Conduction Delay, Joint(s) Pain.

In addition, the following adverse reactions were reported less frequently than 1% either in clinical trials or in marketing experience *(adverse events for marketing experience are given in italics)*. Causality and relationship to propafenone therapy can not necessarily be judged from these events. **Cardiovascular System**: Atrial flutter, AV dissociation, cardiac arrest, flushing, hot flashes, sick sinus syndrome, sinus pause or arrest, supraventricular tachycardia. **Nervous System:** Abnormal dreams, abnormal speech, abnormal vision, *apnea, coma*, confusion, depression, memory loss, numbness, paresthesias, psychosis/mania, seizures (0.3%), tinnitus, unusual smell sensation, vertigo. **Gastrointestinal:** A number of patients with liver abnormalities associated with propafenone therapy have been reported in foreign postmarketing experience. Some appeared due to hepatocellular injury, some were cholestatic and some showed a mixed picture. Some of these reports were simply discovered through clinical chemistries, others because of clinical symptoms. One case was rechallenged with a positive outcome. Cholestasis (0.1%), elevated liver enzymes (alkaline phosphatase, serum transaminases) (0.2%), gastroenteritis, hepatitis (0.03%) **Hematologic**: Agranulocytosis, anemia, bruising, granulocytopenia, *increased bleeding time*, leukopenia, purpura, thrombocytopenia. **Other**: Alopecia, eye irritation, *hyponatremia/inappropriate ADH secretion*, impotence, increased glucose, *kidney failure*, positive ANA (0.7%), *lupus erythematosis*, muscle cramps, muscle weakness, nephrotic syndrome, pain, pruritus.

OVERDOSAGE

The symptoms of overdosage, which are usually most severe within 3 hours of ingestion, may include hypotension, somnolence, bradycardia, intraatrial and intraventricular conduction disturbances, and rarely convulsions and high grade ventricular arrhythmias. Defibrillation as well as infusion of dopamine and isoproterenol have been effective in controlling rhythm and blood pressure. Convulsions have been alleviated with intravenous diazepam. General supportive measures such as mechanical respiratory assistance and external cardiac massage may be necessary.

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Comparison of the Antihypertensive Efficiency of Nitrendipine, Metoprolol, Mepindolol and Enalapril Using Ambulatory 24-Hour Blood Pressure Monitoring

Joachim Schrader, MD, Gerhard Schoel, MD, Heike Buhr-Schinner, MD, Michael Kandt, MD, Gerhard Warneke, MD, Victor W. Armstrong, MD, and Fritz Scheler, MD

In a randomized 6-month study of 201 patients, the antihypertensive efficiency of the calcium antagonist nitrendipine, the β_1-selective blocker metoprolol, mepindolol, the β blocker with intrinsic activity and the angiotensin-coverting enzyme inhibitor enalapril were compared as monitored by 24-hour ambulatory blood pressure (BP) measurements. The study was designed so that a comparable decrease in casual BP values was obtained with all 4 drugs. If normotension was not achieved with monotherapy, a diuretic also was administered. Pretreatment casual BP and mean 24-hour ambulatory BP values did not differ between the 4 groups. Normotension as assessed by casual BP measurements was observed in all 4 groups after 6 months of therapy, there being no significant differences between the groups. However, significantly more diuretics were required in the mepindolol (n = 14) and in the enalapril (n = 20) groups compared to the nitrendipine (n = 5) and metoprolol (n = 7) groups. Despite comparable casual BP control, the 4 groups differed significantly in their mean 24-hour measurements. The greatest systolic and diastolic BP decreases were seen in the metoprolol group. Metoprolol was also the most effective drug in decreasing the frequency of systolic pressure peaks >180 mm Hg. Both β blockers and enalapril significantly decreased the morning BP increase compared to the values before treatment, while nitrendipine did not. These data show that casual BP measurement is not a good predictor of 24-hour BP in patients taking hypertensive therapy. Despite an equal degree of "office" BP control, different antihypertensive regimens do not confer the same degree of "nonoffice" BP control.

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With improvement in technical equipment, noninvasive 24-hour ambulatory blood pressure (BP) determination is now increasingly used to monitor patients with systemic hypertension.[1,2] The underlying reason for such ambulatory monitoring is the large physiologic variability in BP. Casual cuff measurements do not allow one to predict BP behavior during the patients' normal activity.[3–5] Moreover, many patients respond to the doctor's appearance with a rapid increase in BP which can lead to unnecessary treatment with antihypertensive drugs.[6–8] Ambulatory BP monitoring may offer better control of BP in patients taking antihypertensive treatment.[9] However, it is not known whether drugs that show similar antihypertensive effects as assessed by casual BP measurements possess comparable antihypertensive efficacy during ambulatory monitoring. We have therefore performed a randomized study in which 24-hour ambulatory BP monitoring was evaluated in 201 patients with mild to moderate systemic hypertension before and after 6 months of treatment with the calcium antagonist nitrendipine, the β_1-selective blocker metoprolol, the β blocker with intrinsic activity mepindolol or the angiotensin-converting enzyme inhibitor enalapril. All of these drugs had normalized casual BP values as monotherapy or in combination with the diuretic hydrochlorothiazide.

METHODS

Patients were accepted into the study if they had a morning diastolic BP between 95 and 114 mm Hg during 3 casual measurements in the morning on 2 different days. In addition, >20% of BP values had to be >140/90 mm Hg during 24 hours of ambulatory BP monitoring. Patients were either untreated or antihypertensive therapy was discontinued for ≥4 weeks before BP measurements were obtained. Patients with secondary hypertension were excluded. Patients were randomly assigned to 1 of 4 groups treated with either nitrendipine 20 mg (Bayropharm, West Germany), metoprolol 100 mg (Astra, Sweden), mepindolol 5 mg (Schering, West Germany) or enalapril 10 mg (Merck Sharp & Dohme). The doses of the 4 substances were recommended by the companies for all 4 drugs for patients with mild to moderate hypertension and a single daily dose was administered at 8 A.M. Patients whose BP was not <140/90 mm Hg according to a casual BP

TABLE I Patient Characteristics, Casual Blood Pressure Before and Six Months After Therapy and Number of Prescribed Diuretics in the Four Groups

	Nitrendipine n = 50	Metoprolol n = 51	Mepindolol n = 49	Enalapril n = 51
Men	30	32	32	32
Women	20	19	17	19
Age (mean ± SD)	45 ± 15	43 ± 15	41 ± 14	44 ± 13
Casual blood pressure before therapy (mean ± SD)				
Systolic (mm Hg)	159 ± 13	163 ± 16	159 ± 15	163 ± 14
Diastolic (mm Hg)	100 ± 6	101 ± 6	100 ± 5	102 ± 6
Casual blood pressure after 6 months of therapy (mean ± SD)				
Systolic (mm Hg)	128 ± 9	130 ± 12	129 ± 11	133 ± 9
Diastolic (mm Hg)	83 ± 5	84 ± 7	82 ± 7	86 ± 7
No. of prescribed diuretics	5	7	14*	20*

* $p < 0.05$ compared with values in groups 1 and 2.
SD = standard deviation.

determination after 1 and 3 months were also given a diuretic (12.5 mg hydrochlorothiazide). Patients were excluded from the study if normotensive BP values were not achieved with this regimen. Twenty-four-hour BP measurements were repeated after 6 months of treatment in patients with normotensive BP according to casual BP control. Of 456 investigated patients, 299 could be included in the study. Of these 299 patients, 98 were excluded from the final evaluation—47 because of drug-related side effects and 51 because they did not fulfill the protocol. Of 201 patients who were normotensive at the end of the study, 50 were treated with nitrendipine, 51 with metoprolol, 49 with mepindolol and 51 with enalapril. Twenty-four-hour ambulatory BP registration was performed with the unit ICR 5200 (SpaceLabs). Measurements were performed every 15 minutes during the day (6 A.M. to 10 P.M.) and every 45 minutes during the night (10 P.M. to 6 A.M.). With this system,

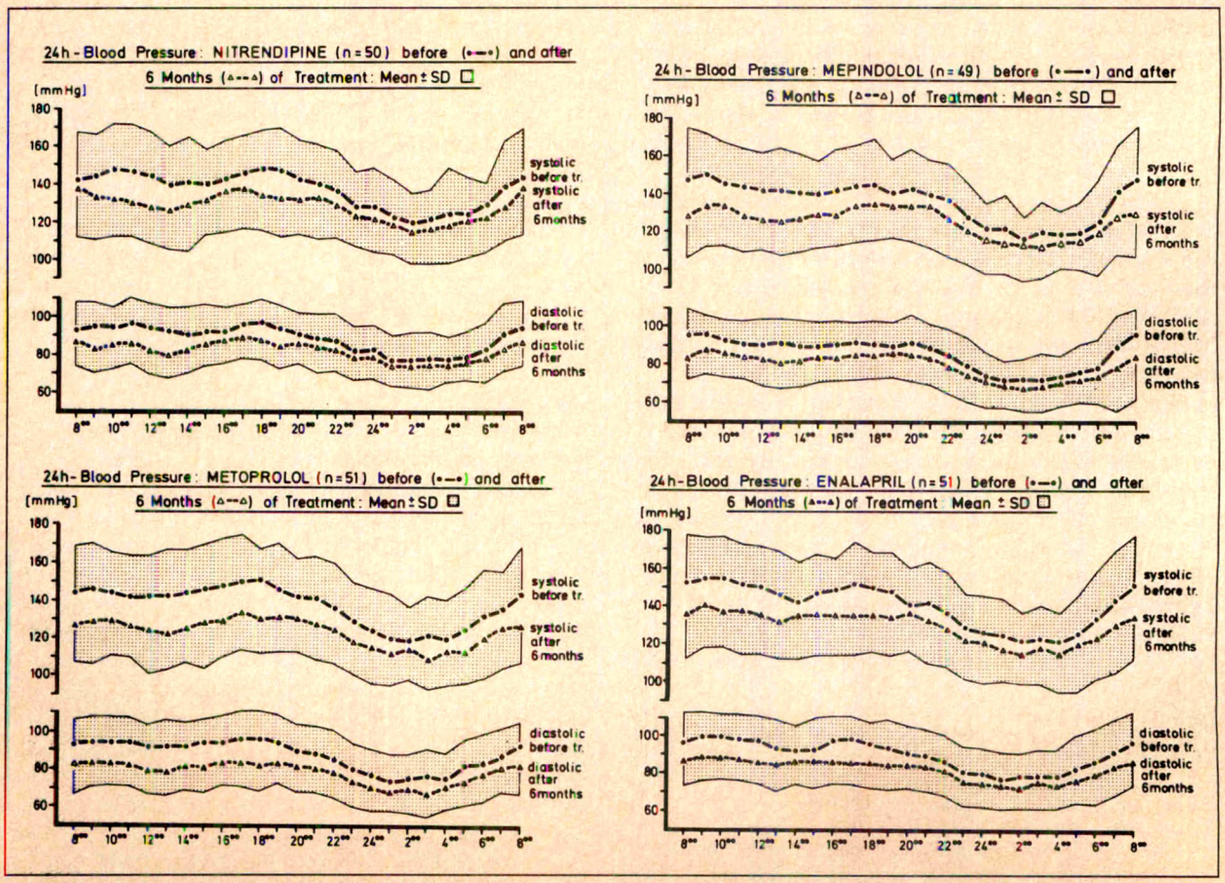


FIGURE 1. Twenty-four-hour blood pressure profiles of the 4 groups before and 6 months after therapy (hourly mean ± standard deviation). tr = treatment.

TABLE II Results of 24-Hour Blood Pressure Measurements

	All Patients		Difference After Six Months Compared with Initial Value				
			All Patients*	Nitrendipine	Metoprolol	Mepindolol	Enalapril
	0	6 Months					
	12,670	12,599	12,670/12,599	3,152/3,240	3,257/3,180	3,090/2,976	3,171/3,202
Mean BP during 24 hours							
Systolic (mm Hg)	139.8	127.8	−12.0	−10.4[2]	−15.0[1,7,8]	−11.1[6]	−11.7[6]
Diastolic (mm Hg)	89.5	81.3	−8.2	−7.6[2]	−10.2[1,3]	−6.9[2]	−8.3
Mean BP 6 A.M. to 10 P.M.							
Systolic (mm Hg)	143.3	130.1	−13.2	−11.6[2]	−16.1[1,7]	−12.0[6]	−13.1
Diastolic (mm Hg)	92.2	83.1	−9.1	−8.6[2]	−11.0[1,3]	−7.5[2]	−9.4
Mean BP 10 P.M. to 6 A.M.							
Systolic (mm Hg)	126.3	118.7	−7.6	−6.0[2]	−10.7[1,7,8]	−6.8[6]	−7.0[6]
Diastolic (mm Hg)	79.2	74.2	−5.0	−3.7[2]	−7.4[1,7,8]	−4.0[6]	−4.8[6]
No. values (%)							
Systolic							
>180 mm Hg	6.8	2.4	−4.4	−3.4[2]	−6.3[1,3,4]	−3.5[2]	−4.3[2]
>160 mm Hg	17.9	6.8	−11.1	−10.4[2]	−12.9[1,3]	−9.2[2,8]	−11.9[7]
>140 mm Hg	44.6	22.7	−21.9	−20.6[2,7]	−24.7[1,4,7]	−21.5[5,6]	−21.3[2]
Diastolic							
>100 mm Hg	22.3	6.2	−16.1	−15.8[2,3,4]	−18.5[1,3]	−10.4[1,2,4]	−19.7
>90 mm Hg	50.3	25.7	−24.6	−25.1[2,7]	−27.5[1,3,4]	−21.4[2,5]	−24.6[2]

* $p < 0.01$ compared with pretreatment values.
1–8: Significant differences between the groups after treatment.
1 = $p < 0.01$, 5 = $p < 0.05$ compared with the nitrendipine group.
2 = $p < 0.01$, 6 = $p < 0.05$ compared with the metoprolol group.
3 = $p < 0.01$, 7 = $p < 0.05$ compared with the mepindolol group.
4 = $p < 0.01$, 8 = $p < 0.05$ compared with the enalapril group.

BP is measured by auscultation with a microphone; if this method fails, BP is registrated by oscillometry. When ambulatory BP measurement was repeated after the treatment period, care was taken so that the patients' activities were comparable to those of the first measurement. With each patient, about 60 to 70 BP values per 24 hours could be analyzed.

Statistics: The frequency of elevated BP values was calculated from all BP values registered during a 24-hour period. Mean values and standard deviations per hour, per 24 hours and for the day and night were also computed. Casual morning BP controls are also given as mean values ± standard deviations. Statistical analyses of the frequency of elevated BP values before and after 6 months of treatment were performed with the chi-square test or Fisher's exact test for discrete variables. BP measurements were compared using nonparametric tests (Wilcoxon rank sum test, Kruskal-Wallis test). Student's *t* test for paired variables was used to test whether the mean difference in the norming BP increase before and after 6 months of therapy was significantly different from zero.

RESULTS

Patient characteristics are listed in Table I. The 4 groups did not differ in age, gender or entry BP values. The morning casual BP values are also listed in Table I. Normotension was observed in all 4 groups after 6 months of treatment; there were no significant differences among the groups. However, the number of patients requiring diuretics to achieve normotension was different—5 patients in the nitrendipine, 7 in the metoprolol, 14 in the mepindolol and 20 in the enalapril group. The first 2 groups differed significantly from the last 2 groups.

The 24-hour BP profiles of all 4 groups are shown in Figure 1. A circadian rhythm was always observed both before and after treatment. The posttreatment mean hourly BP values were lower than the pretreatment values when all 4 drugs were used. The results of the 24-hour ambulatory BP measurements are listed in Table II. Before therapy, 12,670 BP values could be evaluated and after therapy, 12,599 values. The 24-hour mean BP value from all patients decreased by 12 mm Hg systolic and 8.2 mm Hg diastolic after treatment. This decrease was more pronounced from 6 A.M. to 10 P.M. (13.2 systolic and 9.1 mm Hg diastolic) than from 10 P.M. to 6 A.M. (7.6 and 5.0 mmHg). Before treatment, 24-hour BP measurements did not differ significantly among the 4 groups. Despite comparable casual BP control, 24-hour BP measurements differed among the 4 groups. The greatest decreases in mean systolic and diastolic BPs were observed in the metoprolol group (15.0 and 10.2 mm Hg, respectively). Metoprolol reduced systolic BP more significantly during the 24-hour period than the other 3 groups and diastolic BP significantly more than nitrendipine and mepindolol. During the day, metoprolol caused a significantly greater decrease in mean ambulatory BP than either nitrendipine or mepindolol while, during the night, it was also more effective than enalapril. The frequencies of elevated BP values (percent elevated values during 24 hours) also varied. Metoprolol decreased the number of systolic pressure peaks >180 mm Hg more significantly than the other 3 drugs. The greatest decrease in the frequency of systolic values >160 mm Hg was also seen in the metoprolol group

followed by enalapril, nitrendipine and mepindolol. Metoprolol showed a significantly greater decrease of values >140 mm Hg after treatment compared to the other 3 groups. Diastolic values >100 mm Hg were decreased to the greatest extent in the enalapril group followed by metoprolol (both p values <0.01 in comparison to the 2 other groups), whereas mepindolol had the weakest effect. Diastolic values >90 mm Hg decreased to the greatest extent in the metoprolol group followed by nitrendipine and enalapril. Once again, the weakest effect was observed by mepindolol.

The rapid morning increase in BP (difference between the highest morning value before the drug was taken at 8 A.M. and the lowest night time value) also

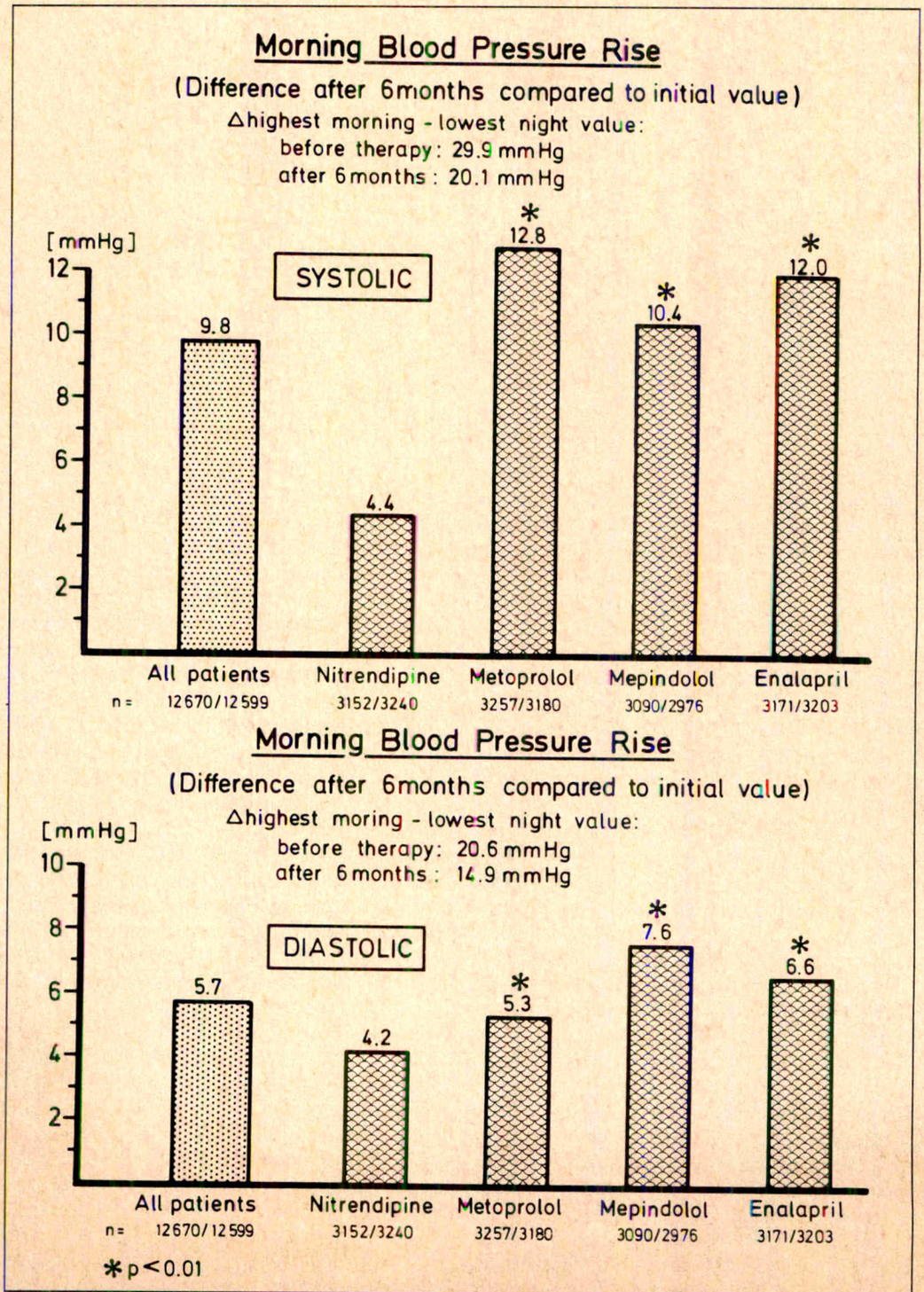


FIGURE 2. Morning blood pressure increase. *Significant differences in comparison to pretreatment values.

showed significant variation. Metoprolol, mepindolol and enalapril significantly decreased the systolic morning increase by 12.8, 10.4 and 12.0 mm Hg, respectively, and the diastolic increase by 5.3, 7.6 and 6.6 mm Hg compared to the values before treatment, whereas nitrendipine had no influence (Figure 2).

DISCUSSION

Twenty-four-hour ambulatory BP monitoring allows an improved assessment of BP and, as speculated by some investigators, of individual cardiovascular risk.[10-12] Perloff et al[13] showed that ambulatory BP values correlate more significantly to cardiovascular events than do casual BP measurements. Ambulatory BP best predicts cardiac end-organ damage and shows a stronger correlation to the incidence of cardiac hypertrophy.[12,14-16]

In this study, we compared the effects of 4 different antihypertensive drugs during 24-hour BP measurements after a 6-month treatment period in which all 4 drugs brought about a similar decrease in casual BP values into the normotensive range.

It could be shown that a similar decrease in casual BP values was not accompanied by a comparable effect during 24-hour BP monitoring. The β_1-selective blocking drug metoprolol exhibited the greatest systolic and diastolic decrease in mean 24-hour BP. This result was not related to an extended time of action, since a significant difference was also evident during the day (6 A.M. to 10 P.M.) when all groups showed antihypertensive effects. It is generally assumed that the cardiovascular damage in hypertension is related to the average level of BP and possibly also to the peaks associated with increased sympathetic activity. Metoprolol caused the greatest decrease in the frequency of elevated systolic values; in particular, systolic pressure peaks >180 mm Hg were 31 to 44% lower in this group compared to the other 3 groups. Whether intermittent BP peaks cause vascular damage in humans remains unproven.[6] However, there is some evidence from animal studies that such peaks can induce vascular damage accompanied by a segmental overstretching of the nonadapted vascular bed.[17,18]

A decrease in the number of hypertensive peaks must therefore be considered as clinically favorable. The number of elevated diastolic values >100 mm Hg decreased most obviously in the enalapril group followed by metoprolol; however, the greater number of diuretics necessary in the enalapril group should be noted. In combination with diurectics, enalapril proved to be an effective therapeutic regimen. Nitrendipine was less effective over 24 hours than metoprolol or enalapril, but required the lowest number of diuretics. The weakest effect on BP, especially on diastolic values, was observed in the mepindolol group despite the large number of diuretics administered.

BP exhibited a circadian rhythm increasing rapidly during the morning hours and then decreasing through a nadir around 3 A.M.[9,19,20] Current evidence suggests a possible link with cardiovascular events that have also been shown to occur most frequently during the morning hours. Stroke, transient ischemia and myocardial infarction all display a circadian rhythm similiar to that shown for arterial BP.[21-23] Although it is only speculation that the rapid increase in early morning BP is a mechanism in cardiovascular events, a role as contributing factor seems possible.[24] As a logical consequence, antihypertensive treatment should provide satisfactory BP control during the critical morning hours when arterial pressure is at its highest. In this study, metoprolol, mepindolol and enalapril significantly decreased the morning BP increase while nitrendipine did not. This might be due to a limited time of action for nitrendipine, and the lowest number of prescribed diuretics in the nitrendipine group must be noted. Other randomized studies dealing with different effects on the morning pressure increase with a sufficient number of treated patients are rare.[24] In all groups, the frequencies of elevated BP values (>140/90 mm Hg) after 6 months of treatment were greater than those of a collective group of normotensive patients investigated using the same methodology.[25] Thus, normotension achieved with antihypertensive therapy differs from "natural" normotension. This could be one explanation for the difference in mortality between treated hypertensive patients and normotensive patients.

The results of this study show that casual BP measurement is not a good predictor of 24-hour BP in patients receiving hypertensive therapy. Different antihypertensive regimens with an equal degree of "office" BP control do not confer the same degree of "nonoffice" BP control. In particular, the frequency of intermittent rapid increase in BP >180 mm Hg systolic and >100 mm Hg diastolic varied greatly among the groups, and there was a difference between the antihypertensive compounds in attenuating the early morning increase in BP. It is not known if an improved efficacy in antihypertensive treatment over 24 hours will improve cardiovascular prognosis in hypertensive patients. However, Wikstrand et al[26] observed a significant decrease in cardiovascular mortality with metoprolol compared to diuretics, despite a similar decrease in casual BP.[26] Although still speculative, an improved control of 24-hour BP may partly explain these differences.

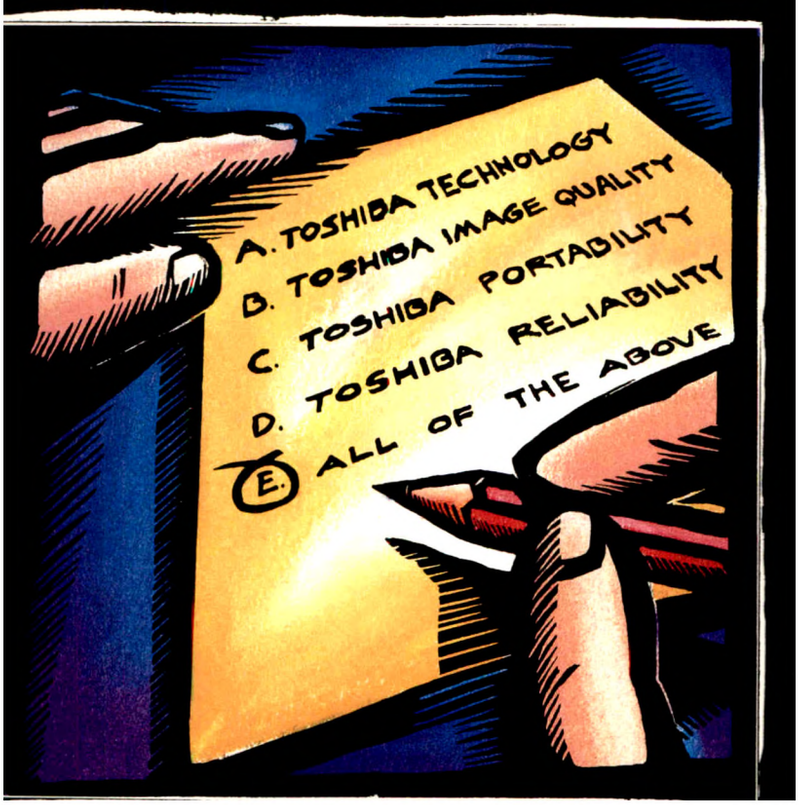
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Expression of Natriuretic Peptide in Ventricular Myocardium of Failing Human Hearts and Its Correlation with the Severity of Clinical and Hemodynamic Impairment

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Atrial natriuretic peptide (ANP) was immunohistochemically investigated in (1) right ventricular endomyocardial biopsy specimens from 87 apparently healthy donor hearts taken from victims of cerebral accidents; (2) 1 normal heart not suitable for transplantation (HBsAg carrier); (3) right ventricular endomyocardial biopsy specimens from 151 patients with dilated cardiomyopathy (DC); and (4) 57 explanted hearts, 26 with DC and 31 with ischemic heart disease. No ANP immunoreactivity was found in normal ventricles. Failing hearts showed ventricular positivity in 31% of the DC biopsy series, in 61% of the left ventricles, and in 30% of the right ventricles of the explanted heart series. An endoepicardial gradient was observed, because ANP positivity was greater and more extensive in the subendocardial layers. Ultrastructural studies were performed on biopsy specimens from 10 normal hearts and 132 DC biopsy samples. No ANP-storing granules were found in biopsy samples of normal ventricles, whereas ANP granules were seen in 15 of 132 (11.4%) DC cases. In parallel immunoblotting, investigation showed the same 13 kDa band protein in 1 normal atrium as well as in 8 failing atria and ventricles. ANP immunoreactivity was positively correlated with higher New York Heart Association functional classes as well as with higher left ventricular end-diastolic pressure ($p < 0.005$), end-diastolic volume ($p < 0.005$) and end-diastolic volume index ($p < 0.005$). In conclusion, apparently healthy ventricles do not show ANP immunoreactivity, whereas failing ventricles do. ANP expression seems to be independent of the underlying disease, but positively related to the clinical status and the degree of left ventricular impairment and dilatation.

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Human atrial myocytes have been shown to contain endocrine granules in which atrial natriuretic peptide (ANP) is stored.[1–4] ANP has also been demonstrated in human fetal ventricles[5–7] and in ventricular conduction tissue of fetal and adult hearts,[8,9] but not in normal human adult ventricles.

In human failing hearts the ANP ventricular genes appear to be reexpressed so that ordinary ventricular myocytes can secrete ANP whatever the underlying disorder.[7,8,10–14] In experimental settings, both pressure and volume ventricular overload may induce ventricular ANP expression.[15–20] Whether ANP ventricular expression in human hearts is conditioned by clinical, metabolic or hemodynamic factors remains to be ascertained. The aim of this study was to: (1) search for ANP immunoreactivity in ventricular myocytes of a large series of failing human hearts, (2) compare the results obtained from diseased hearts with those from normal controls, and (3) correlate ANP ventricular immunoreactivity with the clinical status of the patient and corresponding hemodynamic and angiocardiographic indexes.

STUDY POPULATION

Clinical data from the study groups are summarized in Table I.

Control groups: NORMAL HEART: One apparently healthy donor heart taken from a victim of cerebral trauma was used as control. It was not suitable for cardiac transplantation because it belonged to a chronic HBsAg carrier. Free and septal walls of atria and ventricles, including samples from the apical portion of the right ventricular septum (usual site of endomyocardial biopsy specimens), were sampled. This single observa-

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TABLE I Clinical Data of Patients Investigated

		No. of Pts.	Age (yr) & Sex			Ischemia Time (min)			
Control Groups									
Normal heart		1		M		129			
Normal endomyocardial biopsy samples									
Light microscopy		87/87	29 ± 11	21 F 66 M		127 ± 41			
Electron microscopy		10/87	23 ± 9	9 M 1 F		74 ± 26			
				Length of Disease (mo)		NYHA Class			
	Disease	No. of Pts.	Age (yr) & Sex	From Onset	From CHF	I	II	III	IV
Congestive Heart Failure Groups									
Failing explanted hearts	DC	26	46 ± 13	23 M 3 F	—	24 ± 31	—	—	—	26
	IHD	31	47 ± 11	31 M	79 ± 61	19 ± 7	—	—	—	31
Endomyocardial biopsy samples										
Light microscopy	DC	151	44 ± 11	25 F 126 M	—	35 ± 41	16	44	57	34
Electron microscopy	DC	132	42 ± 16	31 F 101 M	—	22 ± 27	15	43	51	23

Values are expressed as mean ± standard deviation.
CHF = congestive heart failure: DC = dilated cardiomyopathy; IHD = ischemic heart disease; NYHA = New York Heart Association.

tion represents a unique opportunity to study the entire atria and ventricles of a normal viable heart.

NORMAL ENDOMYOCARDIAL BIOPSY SAMPLES: Eighty-seven endomyocardial biopsy specimens of the right ventricle obtained immediately before cardiac implantation from apparently healthy hearts considered suitable for transplantation were tested. Death had occurred from cerebral accidents in 83 cases, and from other causes in 4. Donors received dopamine infusion at doses $<10/\mu g/kg/min$ during the pretransplant period. The apical portion of the right ventricular septum was reached by the bioptome through the exposed right atrium. The 10 biopsy samples with the shortest ischemic time (Table I) were also included in the ultrastructural study. This protocol has already been reported in detail elsewhere.[21]

Congestive heart failure groups: DECOMPENSATED HEARTS: Fifty-seven failing hearts obtained immediately after cardiac explantation were investigated. Twenty-six patients had dilated cardiomyopathy (DC) and 31 had ischemic heart disease.

Samples were obtained from residual atrial cuffs, anterior, lateral and posterior walls of the left ventricle and anterior and posterior walls of the right ventricle. In the group with ischemic disease, the ventricular myocardium was sampled according to the aforementioned topographic criteria in spared areas.

ENDOMYOCARDIAL BIOPSY SAMPLES IN PATIENTS WITH DILATED CARDIOMYOPATHY: Endomyocardial biopsy samples were obtained from each of 151 patients with idiopathic DC.[22] One hundred thirty-two patients also fulfilled the requirements of the electron microscopy protocol (i.e., >1 sample each or a large sample to be subdivided).

METHODS

All patients underwent both right- and left-sided cardiac catheterization, left and right ventriculography and selective coronary angiography with standard techniques. No attempt was made to correlate immunohistochemical results with hemodynamic data in transplanted patients, because variable intervals elapsed between their last hemodynamic angiocardiographic evaluation and cardiac transplant, thus limiting statistical correlation. On the other hand, in the DC biopsy group, hemodynamic and angiocardiographic data were recorded simultaneously with tissue biopsy sampling, thus allowing morphofunctional correlations.

Right ventricular endomyocardial biopsy was performed through the right internal jugular vein, using the Caves-Schultz bioptome according to the Stanford technique. Five to 7 samples were taken from the apical portion of the right interventricular septum as already detailed.[23] Four to 5 samples were processed for light microscopy and 1 to 2 for electron microscopy.

Morphology: LIGHT MICROSCOPY: Samples were immediately fixed in 10% buffered formalin solution, dehydrated and embedded in paraffin. Sections, 5-μm-thick, were stained with hematoxylin-eosin and Masson's trichrome. Immunohistochemical stains were performed on the unstained sections consecutive to those mentioned.

CONVENTIONAL ULTRASTRUCTURAL STUDY: All samples were fixed with 2% glutaraldehyde and 2% formalde-

TABLE II Immunoreactivity of the Left and Right Ventricles in Control and Failing Hearts

	Immunoreactivity to ANP			
	Right Ventricle		Left Ventricle	
	No.	(%)	No.	(%)
Control Groups				
Normal heart	0/1	—	0/1	—
Normal biopsy specimens				
Light microscopy	0/87	—	—	—
Electron microscopy	0/10	—	—	—
Congestive Heart Failure Groups				
Failing explanted hearts				
Dilated cardiomyopathy	8/26	(31)	16/26	(61)
Ischemic heart disease	9/31	(29)	19/31	(61)
DC biopsy samples				
Light microscopy	47/151	(31)	—	—
Electron microscopy	15/132	(11)	—	—

ANP = atrial natriuretic peptide; DC = dilated cardiomyopathy. No. = number of positive cases/cases investigated.

hyde solution in 0.1 M phosphate buffer, pH 7.3 for 2 hours at 4°C. They were then postfixed with 1% osmium tetroxide in 0.1 M cacodilate buffer for 1 hour at 4°C, dehydrated in ethanol and propylene-oxide and embedded in Epon. Ultrathin sections were stained with uranyl acetate and Reynolds's lead citrate.

LIGHT MICROSCOPY IMMUNOHISTOCHEMISTRY: Rabbit polyclonal antialfa-human ANP antibodies (AB 983) were used which recognize the c-terminal sequence of the peptide (Chemicon International, El Segundo, California). Parts of the specimens were also tested using monoclonal antibodies directed against ANP residues 4-28 (CBL 66) (Cymbus, Southampton, United Kingdom; ARNIKA, Milano, Italy) and polyclonal antibodies against synthetic cardiodilatin[24] (a gift from W. G. Forssmann, Dept. of Anatomy, University of Heidelberg, Federal Republic of Germany). Both monoclonal and polyclonal antibodies gave results comparable to those obtained using serum AB 983. The latter was then used throughout the study. Sections were deparaffinized and brought to TRIS phosphate-buffered saline solution (TBS 0.15M, pH 7.35). After blocking endogenous peroxidase with 3% H_2O_2, and pretreatment with type XXVII protease (Sigma Chemicals),[25] the slides were incubated overnight with 1:1000 diluted ANP antiserum. The immunohistochemical staining was performed with the peroxidase-antiperoxidase method[26] and diaminobenzidine was used as chromogen substrate. Specificity tests were performed by absorbing the antiserum with the homologous antigen (10 nmol/ml from Chemicon International, California) or omitting the first layer.[27] Both control tests yielded negative results.

ELECTRON IMMUNOCYTOCHEMISTRY: Ultrathin sections were placed on Parlodion-coated nickel grids of 200 mesh. They were deosmicated by placing them on a droplet of aqueous saturated solution of sodium metaperiodate for 30 min.[28] The sections were then preincubated with 1% ovalbumin in 0.01 M TRIS buffer 0.5 M sodium chloride pH 7.6 (TBS), and subsequently incubated with the ANP antiserum diluted 1:100 with TRIS buffer saline for 12 to 16 hours. The sections were then washed in TRIS buffer saline for 10 minutes 3 times and incubated for 1 hour with protein A-gold complex (Bio Clin, Biochemical Services, Cardiff, United Kingdom) diluted 1:400 with TRIS buffer saline, according to Roth et al[29] and Varndell et al.[30] After three 10-minute washes in TRIS buffer saline, the grids were rinsed in distilled water, dried and stained for 6 minutes with aqueous uranyl acetate (5%) and for 8 minutes with Reynolds's lead citrate. The stained sections were examined with Zeiss EM 9 and EM 902 electron microscopes. Control tests included the substitution of nonimmune rabbit serum with α-ANP antiserum, and adsorption of ANP antiserum with the homologous antigen (10 nmol/ml). All these tests eliminated immunoreactivity.

Immunoblotting: Samples were taken from atria of the normal donor heart and 8 failing explanted hearts (atrial and ventricular walls) of 5 patients with DC and 3 patients with ischemic heart disease. All samples were from failing hearts with positive immunohistochemical reaction with ANP antibodies. Tissue was homogenized

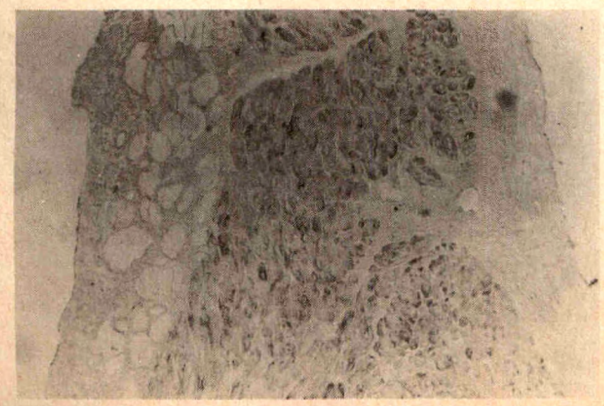


FIGURE 1. Sample from the residual cuff of right atrial wall of an explanted heart from a patient with dilated cardiomyopathy showing diffuse atrial natriuretic peptide immunoreactivity. (PAP method × 80, reduced by 36%).

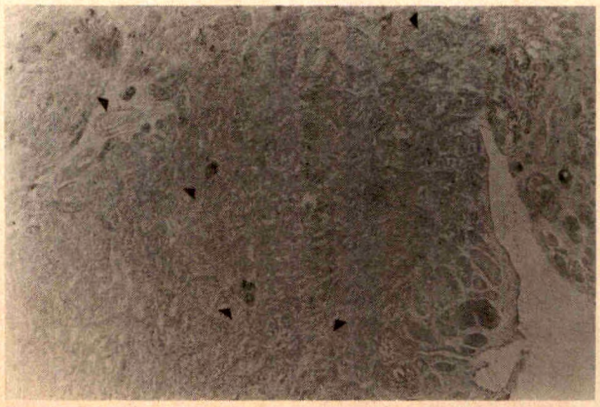


FIGURE 2. Atrial natriuretic peptide immunoreactivity of an explanted heart with dilated cardiomyopathy. Left ventricular wall sample. Atrial natriuretic peptide positivity is indicated by *arrows*. (PAP method × 80, reduced by 36%).

in 3 volumes (vol/wt) of extraction buffer (10 mM phosphate buffer, 140 mM salt: phosphate-buffered solution, pH 7.4, 0.5 mM phenylmethyl sulfonyl fluoride, 500 units/ml aprotinin). The homogenate was then centrifuged for 10 minutes at 10,000 g. The supernatant was brought to sample buffer (62.5 mM TRIS hydroxymethylaminomethane, pH 7.2, 2% sodium dodecyl sulfate, 0.01% bromophenol blue. Twenty microliters of the proteins were heated at 100°C for 5 minutes. Then, sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE, %T = 18%) was performed according to the Laemmli method.[31] Proteins were then transferred to nitrocellulose (BA 83) (Schleicher & Schuell) membranes according to Towbin et al.[32] The electrophoretic blots were soaked in 3% bovine serum albumin in saline (0.9% NaCl/10 mM TRIS-HC1, pH 7.4) for 1 hour at 40°C to saturate additional protein binding sites. They were rinsed in saline and incubated with anti-α-ANP serum AB 983 or anticardiodilatin serum (diluted 1:4000 with TRIS buffer saline) and anti-ANP residues 4–28 (diluted 1:1000 with TRIS buffer saline) for 2 hours at room temperature. Bound antibody was detected with an immune blot kit (Sigma).

Statistical analysis: Data are indicated as mean ± standard deviation. Differences between groups were obtained using chi-square 2 × 2 contingency tables and 2-sample *t* test for unpaired data.

RESULTS

Control groups: Right and left atrial walls of the normal heart showed immunoreactivity for ANP antiserum in histochemical tests, whereas corresponding ventricular wall samples did not. Staining was more intense and diffuse in the subendocardial layers. Positive myocytes had enhanced concentration in perinuclear areas.

None of the 87 right ventricular endomyocardial biopsy specimens taken from normal donor hearts showed immunoreactivity with ANP antiserum. No membrane-bound granules were observed in any of the 10 biopsy specimens from control hearts studied under the electron microscope.

Congestive heart failure groups: immunohistochemistry: EXPLANTED HEARTS: ANP reactivity was present in all residual atrial cuffs of the explanted heart series (Figure 1). ANP immunoreactivity was detected in the majority of the left ventricles of explanted hearts with either DC or ischemic heart disease (Table II, Figure 2). Positive-staining myocytes were mainly located beneath the endocardium either scattered as single cells or clustered in small groups. Positive myocytes immediately beneath endocardium were excluded from evaluation to avoid possible confusion with Purkinje-like cells. ANP immunoreactive material was brown, finely granular and mainly concentrated in perinuclear positions. ANP immunoreactivity in the right ventricle showed a similar morphologic pattern, but it was present in a lower percentage of cases and in fewer cells. Positive myocytes were found in both areas with and without fibrosis (Figure 3). Free walls of right and left ventricles showed a different incidence of positive cells and a similar pattern of immunoreactivity (about 10% of all myocytes in the right ventricle and about 20% in the left ventricle).

DILATED CARDIOMYOPATHY BIOPSY SAMPLES: Forty-seven of the 151 (31%) right ventricular biopsy samples from patients with DC showed ANP reactivity. In all cases, ventricular ANP immunoreactivity was brown, fine and granular. It was distributed in both perinuclear and peripheral areas of single myocytes (Figure 4) or in

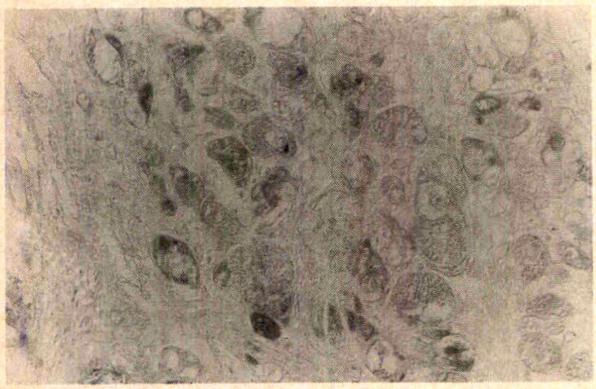


FIGURE 3. Atrial natriuretic peptide positivity in fibrosis area of a heart explanted from a patient with ischemic heart disease. Left ventricular wall sample. (PAP method × 280, reduced by 37%).

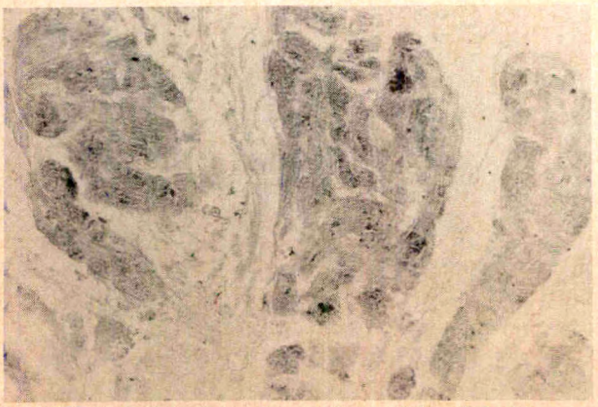


FIGURE 4. Atrial natriuretic peptide positivity of single myocytes of dilated cardiomyopathy endomyocardial biopsy sample. (PAP method × 175, reduced by 35%).



FIGURE 5. Bundle of myocytes showing marked atrial natriuretic peptide immunoreactivity in a dilated cardiomyopathy biopsy sample. (PAP method × 80, reduced by 35%).

small bundles or groups of cells (Figure 5). No immunoreactivity was shown in interstitial cells.

Ultrastructure and immunocytochemistry: Membrane-bound, endocrine-like granules were found in 15 of 132 DC cases investigated (11.4%). They ranged from 100 to 400 nm in size with a slightly dense, finely granular or homogeneous structure. The granules were very few in 13 cases (87%) and abundant in 2 (13%) (Figure 6). These 2 cases did not differ from the remaining 13 positive cases with respect to clinical, hemodynamic and angiocardiographic indexes. The number of myocytes exhibiting this pattern never exceeded 10% of the total myocytes examined. The granules were found both in perinuclear and peripheral areas.

Immunocytochemical investigations with ANP antibodies revealed gold particles specifically distributed over the granules, thus confirming their ANP content (Figure 6).

Immunoblotting: AB 983, cardiodilatin-99-126 and CBL 66 antibodies directed against ANP were found to react strongly with a 13 kDa band protein, in 1 normal atrium as well as in the 8 atria and ventricles of failing hearts.

Dilated cardiomyopathy biopsy group: Correlation of immunohistochemical results with clinical, hemodynamic and angiocardiographic findings: Left ventricular end-diastolic pressure, left ventricular end-diastolic volume, and left ventricular end-diastolic volume index were significantly higher in positive cases than in negative ones (Table III). The left ventricular ejection fraction did not differ among ANP positive and negative cases. The distribution of ANP positive and negative cases among different New York Heart Association (NYHA) classes is listed in Table IV.

Most of the positive cases belonged to NYHA classes III and IV, but ANP positive and negative cases could be found in each class. Therefore, we compared the hemodynamic data of ANP positive and negative cases of patients in NYHA class I and class IV. Results are summarized in Table V. In each class the presence of ANP ventricular immunoreactivity followed the rules derived from analysis of the whole group of failing hearts, so that left ventricular end-diastolic pressure and left ventricular end-diastolic volume were found higher in the ANP positive cases.

DISCUSSION

In our histochemical study, no atrial natriuretic peptide occurred in normal human ventricular wall. Previous immunochemical studies have shown that the ANP content of the left subendocardium in normal adult ventricles is very low (0 to 5 ng/mg protein), if even detectable.[7] Comparable findings concerning the ANP messenger ribonucleic acid content have been obtained in full-thickness right and left free ventricle walls (2% of that in the atria).[10] Such a minute amount of peptide is likely to escape immunohistochemical detection. No immunoreactivity has been documented in a histologically normal heart[8] obtained at postmortem examination or in endomyocardial biopsy specimens from a few patients whose clinical invasive and noninvasive evaluation failed to show any cardiac lesion or dysfunction.[12] These negative results[8] cannot be accepted without reserve since peptide immunoreactivity could have been lost owing to the changes in the postmortem hearts. Moreover, the patients with apparently normal hearts[12] must have had some symptoms in order to undergo invasive evaluation and biopsy. Nevertheless, the results of these studies were confirmed by our observations on a larger series of morphologically and functionally normal hearts explanted from healthy accident victims. Endocrine gran-



FIGURE 6. Immunocytochemical staining of atrial natriuretic peptide. Membrane-bound, endocrine-like granules in dilated cardiomyopathy right ventricular biopsy samples. Gold particles are specifically distributed over the granules. Several positive granules (A) and single atrial natriuretic peptide granule (*arrow*) (B) in 2 different biopsy cases. (A,B × 29,000, reduced by 50%) (B inset ×45,100).

ules were not detected at ultrastructural investigation of 10 donor biopsy specimens with short ischemic time (74 ± 23 minutes). Therefore, it is unlikely that the small amount of ANP detected by radioimmunoassay in normal ventricles[7] is stored in membrane-bound granules as in atrial myocytes.

Our study confirms previous reports[7,8,12–14] suggesting that in failing hearts left and right ventricular myocytes express ANP immunoreactivity independently from the underlying disorders, either DC or ischemic heart disease. We found positive myocytes in 61% of the left ventricles and in 30% of the right ventricles of hearts removed from patients undergoing cardiac transplantation. This percentage of cases with ANP granules observed with electron microscopy (11.4%) is probably due to a smaller sample of tissue investigated with this technique. Synthesis, storage and release mechanisms of ventricular ANP may be partly similar to those found

TABLE III Dilated Cardiomyopathy Biopsy Series: Correlation Between Ventricular ANP Expression and Hemodynamic and Angiocardiographic Data.

	No. of Pts.	Length (mo)	LVEDP (mm Hg)	LVEDV (ml)	LVEDVI (ml/m²)	LVEF (%)
ANP positive group	47	45 ± 40	23 ± 10	499 ± 190	277 ± 100	27 ± 12
ANP negative group	104	31 ± 41	18 ± 10	408 ± 102	225 ± 88	30 ± 12
Statistical significance	—	p <0.05	p <0.005	p <0.005	p <0.005	p <0.1
Total	151	35 ± 41	19 ± 10	432 ± 176	241 ± 95	29 ± 12

Values are expressed as mean ± standard deviation.
ANP = atrial natriuretic peptide; LVEDP = left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction.

TABLE IV Dilated Cardiomyopathy Biopsy Series: Ventricular and Immunoreactivity Versus New York Heart Association Functional Class

		NYHA Class							
		I		II		III		IV	
	n	n	(%)	n	(%)	n	(%)	n	(%)
Light microscopy									
ANP negative group	(104)	13	(12.5)	39	(37.5)	38	(36.5)	14	(13.5)
ANP positive group	(47)	3	(6)	5	(11)	19	(40)	20	(43)
Total	(151)	16	—	44	—	57	—	34	—
Electron microscopy									
ANP negative group	(117)	14	(12)	42	(36)	46	(39)	15	(13)
ANP positive group	(15)	1	(7)	1	(7)	5	(33)	8	(53)
Total	(132)	15	—	43	—	51	—	23	—

Percents are given with respect to the total number of cases in the groups.
ANP = atrial natriuretic peptide; NYHA = New York Heart Association.

TABLE V Dilated Cardiomyopathy Biopsy Series: Plots of Comparison Between Hemodynamic and Angiocardiographic Indexes of ANP Positive and Negative Cases in NYHA Class I (Positive: 18.7%; Negative: 81.3%) or Class IV (Positive: 58.8%; Negative: 41.2%)

			NYHA 1		NYHA 4		p Values*
LVEF (%)	ANP+	NS†	47 ± 8	vs	19 ± 7	NS†	<0.001
	ANP–		38 ± 9	vs	23 ± 11		<0.001
Length of disease (mos)	ANP+	NS†	51 ± 7	vs	62 ± 40	NS†	NS
	ANP–		13 ± 2	vs	64 ± 75		<0.01
LVEDV (ml)	ANP+	NS†	443 ± 234	vs	580 ± 213	p <0.06†	NS
	ANP–		375 ± 110	vs	429 ± 225		NS
LVEDVI (ml/m²)	ANP+	NS†	249 ± 142	vs	323 ± 108	p <0.06†	NS
	ANP–		201 ± 56	vs	260 ± 84		<0.05
LVEDP (mm Hg)	ANP+	NS†	13 ± 5	vs	24 ± 9	NS†	<0.01
	ANP–		15 ± 8	vs	24 ± 11		<0.01

* p values refer to comparison between NYHA class I and IV; † comparison between ANP+ and ANP– cases in the same functional class.
Values are expressed as mean ± standard deviation.
NS = not significant; + = positive; – = negative; other abbreviations as in Table III.

in the atria. In fact, we detected membrane-bound endocrine-type granules in some ventricular myocytes. Storage of ANP in these ventricular granules has been confirmed with the electron immunogold technique.

Our immunoblotting analysis confirms that at least 1 major ANP molecular species is identical to that obtained from normal atria.

ANP expression was found to be more intense and widespread in the subendocardial layers of both normal atria and failing ventricles. An endoepicardial gradient of ANP expression has also been reported in the ventricular wall in early fetal life.[7] ANP reexpression of failing ventricles seems to be characterized by a left to right ratio 1:2. This preferential involvement of left-sided subendocardial layers might be related to the heavier stress of left ventricular subendocardial layers[33] with respect to right ventricular subendocardial layers. Thus, ventricular dilatation and wall stress seem to represent the key stimuli of ventricular ANP reexpression in postnatal life. In addition, plasma ANP levels are increased in patients with congestive heart failure,[34] and a direct correlation has been demonstrated between worsening of clinical conditions and circulating levels of the peptide.[35]

It is not clear why only some of the failing ventricles express ANP. Our biopsy series included consecutive patients in different NYHA functional classes. Our results demonstrate that patients showing ventricular ANP immunoreactivity have significantly higher left ventricular end-diastolic volume and left ventricular end-diastolic pressure than patients with ANP negative ventricles. Therefore, ANP expression by ventricular myocytes seems to respond to the same stimulus that has been shown to increase ANP synthesis in atrial myocytes,[36] i.e., an increase in wall stress. In our study, ANP ventricular immunoreactivity also seems to be associated with a longer duration of disease, but this result should be interpreted with caution because of the frequent inaccuracy in defining onset of disease. Most of the ANP positive cases belonged to NYHA classes III and IV. In oligosymptomatic patients of class I and II, ventricular ANP immunoreactivity seems much less frequent. Specific analysis of ANP positive and negative patients in the class I group shows no difference in left ventricular ejection fraction, left ventricular end-diastolic pressure or left ventricular end-diastolic volume. Class I asymptomatic patients with positive ventricular ANP immunoreactivity are rare, representing only 3 cases in our study population. Statistical analysis is certainly limited by this small number. However, there is a trend toward ANP immunoreactivity as the mean left ventricular end-diastolic volume value progresses, so that the mean left ventricular end-diastolic volume of 443 ml in the NYHA class I/ANP positive is higher than any other ANP negative group, only inferior to the 580 ml value of class IV/ANP positive patients. Thus, increasing values of left ventricular end-diastolic volume seem to correlate with ventricular ANP immunoreactivity, despite severity of symptoms or the degree of left ventricular ejection fraction and left ventricular end-diastolic pressure abnormalities.

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INDICATIONS AND USAGE: ACTIVASE® is indicated for use in the management of acute myocardial infarction (AMI) in adults for the lysis of thrombi obstructing coronary arteries, the reduction of infarct size, the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms.
ACTIVASE® is also indicated in the management of acute massive pulmonary embolism (PE) in adults: for the lysis of acute pulmonary emboli, defined as obstruction of blood flow to a lobe or multiple segments of the lungs, and for the lysis of pulmonary emboli accompanied by unstable hemodynamics, i.e., failure to maintain blood pressure without supportive measures. The diagnosis should be confirmed by objective means, such as pulmonary angiography or noninvasive procedures such as lung scanning.

CONTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding, ACTIVASE® is contraindicated in the following situations: • Active internal bleeding • History of cerebrovascular accident • Recent (within two months) intracranial or intraspinal surgery or trauma (see WARNINGS) • Intracranial neoplasm, arteriovenous malformation, or aneurysm • Known bleeding diathesis • Severe uncontrolled hypertension.

WARNINGS: Bleeding The most common complication encountered during ACTIVASE® therapy is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

Concomitant use of heparin anticoagulation may contribute to bleeding. Some hemorrhagic episodes occurred one or more days after the effects of ACTIVASE® had dissipated, but while heparin therapy was continuing.

As fibrin is lysed during ACTIVASE® therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including sites of catheter insertion, arterial and venous puncture, cutdown and needle puncture).

Intramuscular injections and nonessential handling of the patient should be avoided during treatment with ACTIVASE®. Venipunctures should be performed carefully and only as required.

Should an arterial puncture be necessary during an infusion of ACTIVASE®, it is preferable to use an upper extremity vessel accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding.

Should serious bleeding (not controllable by local pressure) occur, the infusion of ACTIVASE® and any concomitant heparin should be terminated immediately.

Each patient being considered for therapy with ACTIVASE® should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

In the following conditions, the risks of ACTIVASE® therapy may be increased and should be weighed against the anticipated benefits: • Recent (within 10 days) major surgery, e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels • Cerebrovascular disease • Recent (within 10 days) gastrointestinal or genitourinary bleeding • Recent (within 10 days) trauma • Hypertension: systolic BP≥180 mm Hg and/or diastolic BP≥110 mm Hg • High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation • Acute pericarditis • Subacute bacterial endocarditis • Hemostatic defects including those secondary to severe hepatic or renal disease • Significant liver dysfunction • Pregnancy • Diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions • Septic thrombophlebitis or occluded AV cannula at seriously infected site • Advanced age, i.e., over 75 years old • Patients currently receiving oral anticoagulants • Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Arrhythmias Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias are not different from those often seen in the ordinary course of AMI and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when infusions of ACTIVASE® are administered.

Pulmonary Embolism It should be recognized that the treatment of pulmonary embolism with ACTIVASE®, Alteplase, has not been shown to constitute adequate clinical treatment of underlying deep vein thrombosis. Furthermore, the possible risk of reembolization due to the lysis of underlying deep venous thrombi should be considered.

PRECAUTIONS: General Standard management of myocardial infarction or pulmonary embolism should be implemented concomitantly with ACTIVASE® treatment. Noncompressible arterial puncture must be avoided. Arterial and venous punctures should be minimized. In the event of serious bleeding, ACTIVASE® and heparin should be discontinued immediately. Heparin effects can be reversed by protamine.

Readministration There is no experience with readministration of ACTIVASE®. If anaphylactoid reaction occurs, infusion should be discontinued immediately and appropriate therapy initiated.

Although sustained antibody formation in patients receiving one dose of ACTIVASE® has not been documented, readministration should be undertaken with caution.

Laboratory Tests During ACTIVASE® therapy, results of coagulation tests and/or measures of fibrinolytic activity may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. ACTIVASE® is an enzyme that when present in blood in pharmacologic concentrations remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (150-200 units/mL) can to some extent mitigate this phenomenon.

Drug Interactions The interaction of ACTIVASE® with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function (such as acetylsalicylic acid, dipyridamole) may increase the risk of bleeding if administered prior to, during or after ACTIVASE® therapy.

Use of Anticoagulants Heparin has been administered concomitantly with and following infusions of ACTIVASE® to reduce the risk of rethrombosis. Because either heparin or ACTIVASE® alone may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites.

Pregnancy (Category C) Animal reproduction studies have not been conducted with ACTIVASE®. It is also not known whether ACTIVASE® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ACTIVASE® should be given to a pregnant woman only if clearly needed.

Pediatric Use Safety and effectiveness of ACTIVASE® in children has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Short-term studies, which evaluated tumorigenicity of ACTIVASE® and effect on tumor metastases in rodents, were negative.

Studies to determine mutagenicity (Ames test) and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested. Cytotoxicity, as reflected by a decrease in mitotic index, was evidenced only after prolonged exposure and only at the highest concentrations tested.

Nursing Mothers It is not known whether ACTIVASE® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ACTIVASE® is administered to a nursing woman.

ADVERSE REACTIONS: Bleeding The most frequent adverse reaction associated with ACTIVASE® is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

The following incidence of significant internal bleeding (estimated as>250 cc blood loss) has been reported in studies in over 800 patients treated at all doses:

	Total Dose ≤ 100 mg	Total Dose > 100 mg
gastrointestinal	5%	5%
genitourinary	4%	4%
ecchymosis	1%	<1%
retroperitoneal	<1%	<1%
epistaxis	<1%	<1%
gingival	<1%	<1%

The incidence of intracranial bleeding in patients treated with ACTIVASE®, Alteplase, recombinant, is as follows:

Dose	Number of Patients	%
100 mg	3272	0.4
150 mg	1779	1.3
1-1.4 mg/kg	237	0.4

These data indicate that a dose of 150 mg of ACTIVASE® should not be used because it has been associated with an increase in intracranial bleeding.

Recent data indicate that the incidence of stroke in 6 randomized double-blind placebo controlled trials[1-7] is not signficantly different in the ACTIVASE® treated patients compared to those treated with placebo (37/3161, 1.2% versus 27/3092, 0.9%, respectively) (p = 0.26).

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, ACTIVASE® therapy should be discontinued immediately, along with any concomitant therapy with heparin.

Fibrin, which is part of the hemostatic plug formed at needle puncture sites, will be lysed during ACTIVASE® therapy. Therefore, ACTIVASE® therapy requires careful attention to potential bleeding sites.

Allergic Reactions No serious or life-threatening allergic reactions have been reported. Other mild hypersensitivity reactions such as urticaria have been observed occasionally.

Other Adverse Reactions Other adverse reactions have been reported, principally nausea and/or vomiting, hypotension, and fever. These reactions are frequent sequelae of MI and may or may not be attributable to ACTIVASE® therapy.

DOSAGE AND ADMINISTRATION: ACTIVASE® is for intravenous administration only. **ACUTE MYOCARDIAL INFARCTION: Administer ACTIVASE® as soon as possible after the onset of symptoms.**

The recommended dose is 100 mg administered as 60 mg (34.8 million IU) in the first hour (of which 6 to 10 mg is administered as a bolus over the first 1-2 minutes), 20 mg (11.6 million IU) over the second hour, and 20 mg (11.6 million IU) over the third hour. For smaller patients (less than 65 kg), a dose of 1.25 mg/kg administered over 3 hours, as described above, may be used.[8]

Although the use of anticoagulants and antiplatelet drugs during and following administration of ACTIVASE® has not been shown to be of unequivocal benefit, heparin has been administered concomitantly for 24 hours or longer in more than 90% of patients. Aspirin and/or dipyridamole have been given either during and/or following heparin treatment.

PULMONARY EMBOLISM: The recommended dose is 100 mg administered by intravenous infusion over two hours. Heparin therapy should be instituted or reinstituted near the end of or immediately following the ACTIVASE® infusion when the partial thromboplastin time or thrombin time returns to twice normal or less.

A DOSE OF 150 MG OF ACTIVASE® SHOULD NOT BE USED BECAUSE IT HAS BEEN ASSOCIATED WITH AN INCREASE IN INTRACRANIAL BLEEDING.

Reconstitution and Dilution DO NOT USE IF VACUUM IS NOT PRESENT.

ACTIVASE® should be reconstituted by aseptically adding the appropriate volume of the accompanying Sterile Water for Injection, USP to the vial. It is important that ACTIVASE® be reconstituted only with Sterile Water for Injection, USP without preservatives. Do not use Bacteriostatic Water for Injection, USP. The reconstituted preparation results in a colorless to pale yellow transparent solution containing ACTIVASE® 1.0 mg/mL at approximately pH 7.3. The osmolality of this solution is approximately 215 mOsm/kg.

Because ACTIVASE® contains no antibacterial preservatives, it should be reconstituted immediately before use. The solution may be used for intravenous administration within 8 hours following reconstitution when stored between 2-30°C. Before further dilution or administration, the product should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

ACTIVASE® may be administered as reconstituted at 1.0 mg/mL. As an alternative, the reconstituted solution may be diluted further immediately before administration in an equal volume of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to yield a concentration of 0.5 mg/mL. Either polyvinyl chloride bags or glass bottles are acceptable. ACTIVASE® is stable for up to 8 hours in these solutions at room temperature. Exposure to light has no effect on the stability of these solutions. Excessive agitation during dilution should be avoided; mixing should be accomplished with gentle swirling and/or slow inversion. Do not use other infusion solutions, e.g., Sterile Water for Injection, USP or preservative-containing solutions for further dilution.

No other medication should be added to infusion solutions containing ACTIVASE®. Any unused infusion solution should be discarded.

HOW SUPPLIED: ACTIVASE® is supplied as a sterile, lyophilized powder in 20 mg and 50 mg vials containing vacuum, each packaged with diluent for reconstitution.

Storage Store lyophilized ACTIVASE® at controlled room temperature not to exceed 30°C (86°F), or under refrigeration (2-8°C/36-46°F). Protect the lyophilized material during extended storage from excessive exposure to light.

Do not use beyond the expiration date stamped on the vial.

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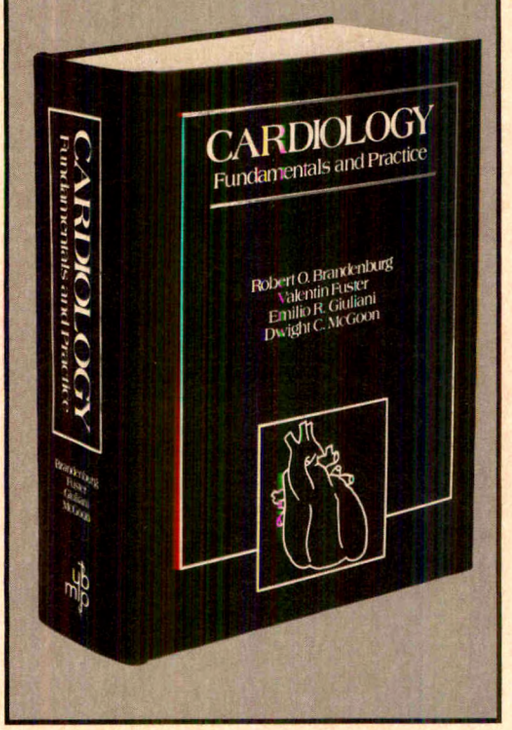
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Usefulness of Verapamil for Congestive Heart Failure Associated with Abnormal Left Ventricular Diastolic Filling and Normal Left Ventricular Systolic Performance

John F. Setaro, MD, Barry L. Zaret, MD, Douglas S. Schulman, MD, Henry R. Black, MD, and Robert Soufer, MD

Normal left ventricular systolic performance with impaired left ventricular diastolic filling may be present in a substantial number of patients with congestive heart failure (CHF). To evaluate the effect of oral verapamil in this subset, 20 men (mean age 68 ± 5 years) with CHF, intact left ventricular function (ejection fraction >45%) and abnormal diastolic filling (peak filling rate <2.5 end-diastolic volumes per second [edv/s]) were studied in a placebo-controlled, double-blind 5-week crossover trial. All patients underwent echocardiography to rule out significant valvular disease, and thallium-201 stress scintigraphy to exclude major active ischemia. Compared to baseline values, verapamil significantly improved exercise capacity by 33% (13.9 ± 4.3 vs 10.7 ± 3.4 minutes at baseline) and peak filling rate by 30% (2.29 ± 0.54 vs 1.85 ± 0.45 edv/s at baseline) (all p <0.05). Placebo values were 12.3 ± 4.0 minutes and 2.16 ± 0.48 edv/s, respectively (difference not significant for both). Improvement from baseline in an objective clinicoradiographic heart failure score (scale 0 to 13) was significantly greater with verapamil compared to placebo (median improvement in score: 3 vs 1, p <0.01). Mean ejection fraction and systolic blood pressure were unchanged from baseline; diastolic blood pressure and heart rate decreased to a small degree. Verapamil may have therapeutic efficacy in patients with CHF, preserved systolic function and impaired diastolic filling.

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It is well recognized that clinical manifestations of congestive heart failure (CHF) may occur in the presence of intact left ventricular systolic performance.[1–6] This subset of patients with normal systolic function may encompass as many as 30 to 40% of patients with CHF referred for noninvasive evaluation[1,3,6] and therefore represents a substantial population. When common mechanisms such as volume overload or valvular regurgitation can be excluded, the cause of CHF is presumed to be diastolic dysfunction. In studies where this has been evaluated noninvasively, abnormal diastolic filling has been shown by either radionuclide or echocardiographic techniques.[1,3,4]

Therapy for patients with CHF and intact systolic and impaired diastolic performance has not been well defined. Verapamil and other calcium antagonists have been used in patients with hypertrophic cardiomyopathy and impaired diastolic filling.[7–14] The use of calcium antagonists in these patients has resulted in clinical improvement as well as in improved diastolic filling. Consequently, we performed a placebo-controlled crossover trial to assess the effects of verapamil in patients with CHF, preserved left ventricular systolic performance and abnormal diastolic filling. Patients were evaluated by an objective clinicoradiographic scoring system, treadmill exercise performance and radionuclide measures of left ventricular filling and ejection fraction.

METHODS

Patient population: The 20-patient study group was selected prospectively from patients with CHF referred for evaluation in the nuclear cardiology laboratory of the West Haven Veterans Administration Medical Center. Criteria for entry were unequivocal clinical CHF for >3 months, preserved left ventricular systolic performance, as defined by radionuclide left ventricular ejection fraction >45%, and abnormal left ventricular peak filling rate (>2.5 end-diastolic volumes per second [edv/s]). CHF was graded by a clinicoradiographic scoring system modified from Lee et al,[15] and used earlier by our group in the assessment of diastolic CHF.[1] Points were assigned for increasing grades of dyspnea, pulmonary congestion on physical examination, neck vein distention, third heart sound, peripheral edema, and CHF on an independently read chest film. The maximum score possible was 13, signifying the most severe CHF. Patients were excluded if they had sustained

a myocardial infarction within 3 months, had angina pectoris, significant valvular disorders (stenotic lesions or regurgitant lesions >1 + severity on a scale of trace to 4+), asymmetric hypertrophic heart disease (septal/posterior wall thickness >1.5) by echocardiography, valve replacement, bradycardia or atrioventricular conduction delay, pacemaker, complex ventricular ectopic activity, therapy with afterload reducers or calcium antagonists, severe obstructive lung disease (forced expiratory volume in 1 second ≤1.5 liters), or hepatic or renal insufficiency.

Protocol: After informed consent was obtained, eligible patients receiving digoxin had this therapy stopped 7 days before starting the protocol.[16] Diuretics were continued at a constant dosage throughout. Baseline evaluation included CHF score, treadmill exercise testing on a modified Naughton protocol,[17] and radionuclide measurement of global left ventricular ejection fraction by gamma camera equilibrium radionuclide angiocardiography, followed by a non-imaging nuclear probe study to evaluate peak filling rate.[1] Patients also underwent screening with thallium-201 stress scintigraphy and 2-dimensional and M-mode echocardiography at initial evaluation to rule out major occult ischemic and valvular heart disease, respectively. After initial screening and baseline evaluation, patients were placed in a random double-blind fashion on either placebo or verapamil 80 mg 3 times daily for 1 week (Figure 1). If tolerated, the verapamil dosage was increased to 120 mg 3 times daily by another investigator unaware of the initial therapy. If not tolerated, the dosage was lowered to 80 mg twice daily. Placebo doses were also increased. After 2 weeks of treatment, patients were reevaluated by the blinded investigator, with repeat clinical examination and CHF grading, exercise testing, radionuclide angiocardiogram and nuclear probe study. The initial study period was followed by a 4-day washout interval, after which patients were crossed over into the opposite arm of the study. At the conclusion of the second period patients were similarly reevaluated clinically by the blinded investigator and again underwent full laboratory assessment.

Radionuclide techniques: Left ventricular ejection fraction was determined in a standard manner using equilibrium radionuclide angiocardiography and a modified in vivo labeling technique.[1] To analyze peak filling rate, a high temporal resolution non-imaging nuclear probe was used.[1] As previously described, this device provides high temporal resolution as well as the sensitivity necessary for the evaluation of the diastolic filling phase of the left ventricle. The peak filling rate, reflecting the maximal rate of change in counts during early to mid-diastole (normal >2.5 edv/s), has been used in several laboratories as an index of diastolic performance.[1,10,18] Equilibrium and probe studies were read separately by independent observers, each unaware of the clinical situation.

Thallium-201 scintigraphy was performed with either treadmill exercise or pharmacologic stress with intravenous or oral dipyridamole. Stress and delayed images were processed for computer quantification using a standard technique.[19] Visual interpretations were confirmed by quantitative distribution profile analysis.

Echocardiography and chest radiography: M-mode and 2-dimensional echocardiograms with conventional and color flow Doppler were interpreted without knowledge of clinical circumstances. Chest films were read independently by a radiologist. Each film was evaluated for pulmonary vascular congestion.

Statistical analysis: Data are expressed as mean ± standard deviation, and were evaluated by paired *t* tests and analysis of variance, with corrections for multiple comparison. Dunnett's test was then used to compare 2 treatment options to a single control. Because it is a non-continuous variable, CHF score was evaluated in terms of degree of change from baseline using Wilcoxon's paired signed rank sum test. A p value <0.05 was considered significant. Regression analysis was used in examining correlations between variables.

RESULTS

Patient characteristics: Twenty-two patients entered the study. One did not complete the study because of noncompliance, and a second developed a supraventricular tachyarrhythmia in the placebo phase and was treated with verapamil. Twenty patients completed the study. Their mean age was 68 ± 5 years (range 59 to 79). All were men and 4 were black. Six had a past history of severe CHF (pulmonary edema). Fifteen had a history of hypertension. Five patients (including 2 who

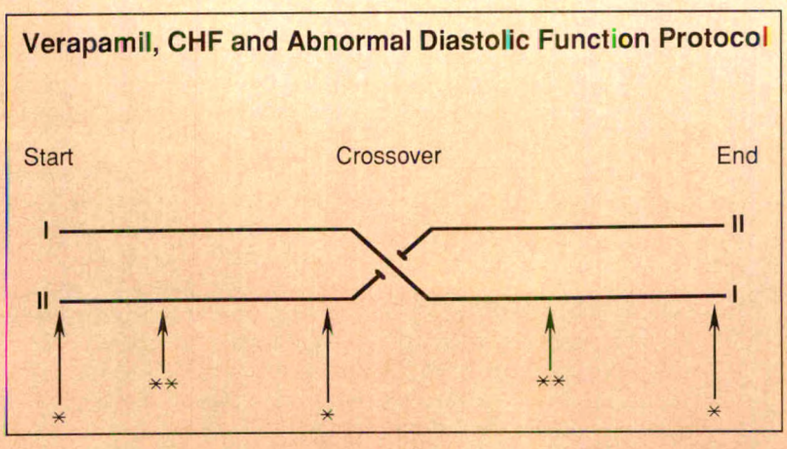


FIGURE 1. Protocol for crossover study of verapamil, congestive heart failure and abnormal diastolic function. Groups I and II received verapamil and placebo, respectively, and then crossed over to the alternate treatment. Evaluations (*) by congestive heart failure (CHF) score, exercise treadmill test, left ventricular ejection fraction, peak filling rate and dosage adjustment (**) were conducted at the time points shown.

were also hypertensive) had clinical evidence of underlying coronary artery disease: 3 had had coronary bypass surgery, 1 had had a successful single vessel coronary angioplasty, and 1 had electrocardiographic evidence of a clinically undated myocardial infarction. Two patients had neither coronary disease nor hypertension. Three had been treated with digoxin and diuretics, 14 with diuretics alone. Seven patients had diabetes mellitus requiring therapy. Three patients had mild renal insufficiency (serum creatinine 1.5 to 3.0 mg/dl). All patients had a forced expiratory volume in 1 second of >1.5 liters.

Total patients screened: Between January 1986 and July 1988, 419 patients with a diagnosis of CHF of ≥3 months' duration were screened. Of these, 182 (43%) had preserved systolic function as assessed by radionuclide ejection fraction >45%. Of the 160 patients who did not participate in the study, 38 were ineligible because of competing therapy, including calcium antagonists, afterload reducers or experimental agents. Forty-five were excluded for reasons relating to cardiac rhythm, including bradycardia, abnormal atrioventricular conduction, pacemaker or complex ventricular ectopy. Because of evidence of active myocardial ischemia or infarction within 6 months, 56 were ineligible, and 10 did not enter because of significant valvular disease. Twelve patients were excluded because of recent general surgery, psychiatric disorders, lung disease, renal or hepatic failure, and refusal or inability to give consent.

Stress scintigraphy and echocardiographic screening: To exclude major active ischemia as a cause for impaired diastolic function, screening thallium-201 stress scintigraphy was done in 19 of 20 patients. One patient had a normal coronary arteriogram within 6 months of the trial with no change in clinical status and thallium-201 study was therefore not performed. In capable patients (n = 12) a treadmill exercise thallium study was performed. In the 8 patients unable to exercise because of noncardiac reasons, dipyridamole thallium-201 scintigraphy was done. All tests were negative for inducible chest pain or electrocardiographic findings. Seventeen of 19 patients had no reversible thallium defects. Two patients had small reversible defects that were not associated with symptoms. The perfusion defects observed in these 2 patients represented extremely small zones of apparent hypoperfusion involving only the inferoapical segment and seen in only 1 view. These defects were judged to be of limited functional significance.

All patients underwent echocardiography to assess wall thickness and valvular function. Of 16 patients in whom technically adequate studies could be obtained, 13 had symmetric left ventricular hypertrophy, defined as wall thickness >1.2 cm. All hypertrophic patients had a history of hypertension. For the entire group, the mean wall thickness was 1.4 ± 0.4 cm (range 1.0 to 2.3). None had asymmetric hypertrophy, defined as septum to posterior wall thickness ratio >1.5 , or significant regurgitant valvular disease by color flow, defined as >1+ on a scale of trace to 4+.

Verapamil dosage: The mean daily total dose of verapamil was 256 mg (range 160 to 360 mg). Bradycardia or asymptomatic atrioventricular conduction delay prevented maximization of dose (360 mg) in most patients. Occasional, mild episodes of constipation occurred in 5 patients. Otherwise, verapamil was well tolerated, without any cardiovascular complications.

Ejection fraction: The left ventricular ejection fraction remained constant throughout the trial. At baseline, the mean ejection fraction was 60 ± 9%; the active treatment and placebo values were 62 ± 8%, and 60 ± 10%, respectively (difference not significant for both versus baseline) (Table I).

Congestive heart failure score: Mean baseline CHF score was 6.7 ± 1.7. After verapamil therapy, CHF score decreased significantly to 3.8 ± 1.6 vs 6.1 ± 1.9 with placebo, a median improvement in CHF score of 3 versus 1 with placebo ($p < 0.01$ by Wilcoxon's paired signed rank sum test). When normalized to evaluate change, the verapamil value was also significant (Table I).

Exercise data: In the 12 patients capable of exercise, there was an increase in mean exercise time of 33% (13.9 ± 4.3 vs 10.7 ± 3.4 minutes at baseline) with verapamil therapy ($p < 0.05$). With placebo, the mean value for the group increased only 15% (to 12.3 ± 4.0 minutes) (difference not significant versus baseline). By *t* test, exercise time while receiving verapamil was significantly greater when compared directly to placebo ($p < 0.01$) (Table I).

Peak filling rate: Mean baseline peak filling rate was 1.85 ± 0.45 edv/s (range 0.96 to 2.47) and as a major selection criterion was abnormal in all. It increased 30% (to 2.29 ± 0.54 edv/s) after verapamil therapy ($p < 0.05$). The peak filling rate in 6 of 20 patients entered the normal range (>2.5 edv/s) after verapamil. Peak filling rate with placebo was 2.16 ± 0.48 edv/s (difference not significant versus baseline) (Table I). When peak filling rate with verapamil was directly compared to peak filling rate with placebo (*t* test), the difference was not significant. In addition, the cohort receiving verapamil before placebo showed a trend toward persistence of improvement in peak filling rate into the placebo phase (baseline 1.66, increasing to 2.14 with verapamil, remaining at 2.07 edv/s with placebo, both significantly different from baseline, $p < 0.05$). This phenomenon, which was not present in the subgroup of patients receiving placebo initially, suggests a favorable effect on ventricular filling persisting beyond pharmacologic expectation.

Despite the significant improvement in CHF score, exercise capacity and peak filling rate over baseline seen in patients treated with verapamil, there were no correlations among the changes seen in these parameters. No strong correlation was found between change in peak filling rate and left ventricular wall thickness.

Blood pressure and heart rate: Systolic blood pressure at rest did not change significantly with placebo or active treatment (Table I). Mean baseline systolic pressure was 146 ± 18 mm Hg (range 120 to 180); with verapamil it decreased to 136 ± 16 mm Hg (range 112 to 170) (difference not significant). Average systolic blood pressure with placebo was 139 ± 21 mm Hg (range 110 to 198) (difference not significant). Diastolic

TABLE I Comparison of Congestive Heart Failure Severity, Exercise Capacity, Peak Filling Rate, Left Ventricular Ejection Fraction, Blood Pressure and Heart Rate Parameters Among 20 Patients at Baseline, with Placebo and with Verapamil

		CHFS			Ex Cap (min)			PFR (edv/s)			LVEF (%)				BP (mm/Hg)			HR (beats/min)		
Pt	Dx	B	P	V	B	P	V	B	P	V	B	P	V		B	P	V	B	P	V
1	X	6	7	4	6.50	7.10	8.10	1.16	2.50	2.42	58	61	71		170/80	166/82	150/80	58	60	66
2	H	6	5	5	6.35	7.00	8.10	2.21	2.71	2.01	53	59	55		180/85	198/92	146/80	60	68	54
3	H, C	7	7	5	12.00	10.80	12.70	1.60	1.60	2.24	49	42	51		135/80	140/92	130/80	70	78	68
4	C	7	5	3	12.00	12.70	13.90	1.57	1.59	1.60	48	45	42		158/82	128/82	135/80	76	80	70
5	H	7	6	4	14.00	16.00	17.20	1.98	1.82	1.88	67	63	60		124/84	118/72	112/72	82	76	74
6	H	3	2	1	16.00	16.10	21.50	1.57	1.91	2.49	58	55	62		156/96	146/86	142/84	82	78	74
7	H	7	6	4	13.90	14.00	17.00	1.57	1.49	2.17	67	63	63		160/70	150/76	148/70	78	78	70
8	H, C	7	5	4	6.90	7.10	10.70	1.99	2.45	2.10	63	78	73		166/88	124/78	134/78	82	78	66
9	H	6	5	3	13.20	18.30	17.00	1.99	2.56	2.41	60	66	61		148/82	144/75	138/72	80	82	70
10	H	9	9	8	—	—	—	1.34	2.43	1.79	46	40	44		132/82	128/90	126/80	114	108	112
11	H	8	7	4	—	—	—	2.06	1.57	2.27	66	69	72		134/90	110/70	122/70	88	80	76
12	H	6	5	4	—	—	—	1.29	2.46	2.55	59	50	62		165/85	166/82	166/84	80	76	70
13	H	3	2	1	—	—	—	2.33	1.84	3.21	53	59	62		130/80	126/88	120/82	76	76	70
14	C	9	6	4	10.00	11.10	10.00	0.96	1.71	1.82	50	61	60		128/80	118/80	118/78	78	70	74
15	H	8	9	4	—	—	—	2.27	1.94	2.66	75	69	73		150/80	140/70	125/70	80	80	68
16	H	7	7	3	—	—	—	2.11	3.00	3.93	58	60	65		130/86	138/80	130/78	80	78	68
17	X	7	8	5	11.40	17.00	18.50	2.04	3.00	2.47	70	70	63		132/88	128/80	170/95	88	84	73
18	H	10	9	6	—	—	—	1.98	2.17	2.19	65	64	64		120/86	120/78	120/80	80	88	64
19	C	6	6	3	—	—	—	2.50	2.66	2.11	65	69	66		135/80	138/80	134/78	80	70	68
20	H	5	6	2	6.50	10.00	12.50	2.47	1.88	1.61	65	60	65		160/95	166/100	160/90	68	72	65
Mean		6.7	6.1	3.8	10.7	12.3	13.9	1.85	2.16	2.29	60	60	62	SBP	146 ± 18	139 ± 21	136 ± 16	79 ± 11	78 ± 9	71 ± 11
± SD		± 1.7	± 1.9	± 1.6	± 3.4	± 4.0	± 4.3	± 0.45	± 0.48	± 0.54	± 9	± 10	± 8	DBP	84 ± 6	82 ± 8	79 ± 6			

B = baseline; BP = blood pressure; C = coronary artery disease; CHFS = congestive heart failure score; DBP = diastolic blood pressure; Dx = presumed diagnosis; Ex Cap = exercise capacity; H = hypertensive heart disease; HR = heart rate; LVEF = left ventricular ejection fraction; P = placebo; PFR = peak filling rate; Pt = patient; SBP = systolic blood pressure; SD = standard deviation; V = verapamil; X = uncertain; — = incapable of exercise.

pressure decreased with verapamil from 84 ± 6 mm Hg (range 70 to 96) at baseline to 79 ± 6 mm Hg (range 70 to 95) ($p < 0.05$), and remained with placebo at 82 ± 8 mm Hg (range 70 to 100) (difference not significant). Heart rate decreased with verapamil from 79 ± 11 beats/min (range 58 to 114) at baseline to 71 ± 11 beats/min (range 54 to 112) with active therapy ($p < 0.05$). With placebo, heart rate was unchanged (78 ± 9 beats/min, range 60 to 108, difference not significant). At peak exercise, there were no differences in heart rate or systolic blood pressure. Peak heart rate values for baseline, placebo, and verapamil were 123 ± 29, 125 ± 23, and 124 ± 21 beats/min, respectively (difference not significant), and peak systolic blood pressure values were 185 ± 15, 186 ± 22, and 177 ± 23 mm Hg, respectively (difference not significant).

DISCUSSION

In this prospective study, we have shown that oral verapamil is effective in improving short-term clinical status, exercise capacity and diastolic filling in patients with CHF, normal systolic performance and abnormal diastolic filling. Few side effects occurred and systolic performance was unchanged. This study also points out the therapeutic value of characterizing left ventricular performance in CHF patients. The absence of significant valvular disease and observable major ischemia, viewed in the context of abnormal left ventricular filling, strongly suggests that CHF resulted from impaired diastolic performance. The exclusion of patients with confounding variables such as valvular disease, active myocardial ischemia, arrhythmias, lung disease, and other medical conditions reflects an effort to direct primary attention to abnormalities of diastolic filling. This served to ensure a focused study group appropriate to the investigative questions being posed. It is likely, however, that up to three-fourths of the excluded patients were suitable for clinical administration of the drug, especially those with ischemia, supraventricular tachyarrhythmias or lung disease. With careful dosing, renally or hepatically impaired patients could be treated as well. It should be emphasized that our study was carried out only for a short duration and involved a homogeneous cohort. Further studies are clearly indicated, involving more patients and emphasizing long-range outcome and survival.

Prevalence of the syndrome: Since the advent of non-invasive means of evaluating ventricular function, several centers have reported classic CHF and preserved left ventricular systolic performance.[1–6] Earlier, we noted that this group may comprise up to 40% of patients referred for the evaluation of CHF.[1] Common underlying clinical diagnoses are atherosclerotic heart disease and hypertension.[20,21] We observed that 62% of such patients with CHF and normal systolic performance had abnormal or borderline diastolic function.[1] Other investigators have found hypertensive heart disease to be an important predisposition in their CHF patients with normal systolic function.[2,3,5] Topol et al[4] noted similar findings in older hypertensives and coined the term "hypertensive hypertrophic cardiomyopathy of the elderly." In selected patients, they retrospectively found improvement of CHF with calcium antagonists, and poor outcome with vasodilators. Marantz et al[6] reaffirmed the presence of clinical CHF despite normal ejection fraction by radionuclide study in 407 patients with a large prevalence of hypertension and coronary artery disease. Between 34 and 40% of their patients satisfied CHF criteria despite normal systolic function.

Use of verapamil: To our knowledge, no study to date has addressed the question of optimal therapy for patients with the characteristics described in this report. However, the syndrome we describe bears a similarity to hypertrophic cardiomyopathy, where diastolic filling tends to be abnormal and where verapamil has improved patient symptoms and exercise capacity, with reduction in left ventricular mass, and augmentation of parameters of diastolic filling in short- and long-term trials.[7–10] Studies in hypertrophic cardiomyopathy patients using more limited outcome endpoints have noted improvement in diastolic properties with nifedipine[11,12] and diltiazem.[15,16] In addition, verapamil was selected for this study because of its relatively greater effect on myocardial cell calcium flux and lesser effect on coronary vasodilation and systemic afterload reduction in comparison with diltiazem and nifedipine.[22]

The present study has several limitations. We examined an exclusive, small group of older men. Patients appeared not to return fully to baseline diastolic filling state when given placebo. This trend may be explained by what has been described previously in crossover trials as a "time-treatment" interaction, in which the effect of active therapy given first may endure beyond several pharmacologic half-lives to influence findings in the placebo phase. In our trial, this effect could result from an action of verapamil that confers long-term benefit on patients with impaired ventricular filling. In a recent study using verapamil in elderly hypertensives with left ventricular hypertrophy, Schulman et al[21] found a persistence of improved diastolic filling 2 weeks after stopping verapamil in patients who had experienced regression of hypertrophy. In our study, a trend toward persistence of normalization of diastolic filling was apparent in patients who had received verapamil before placebo, supporting this hypothesis. Alternatively, the baseline state of chronic decompensated heart failure may require weeks or months to reappear after active therapy ceases.

The lack of correlation between changes in peak filling rate and clinical status is of interest and may have several explanations. Peak filling rate obtained by radionuclide or other methods is not a full reflection of left ventricular diastolic performance.[23,24] Diastolic performance is a complex phenomenon involving ventricular relaxation, compliance, preload, atrial function, afterload, and coronary vascular influences; a single volumetric measurement such as peak filling rate may not be sufficiently descriptive.[23–25] Alternatively, peak filling rate may simply be a marker for other processes not currently well understood. Nevertheless, it has been use-

ful in the characterization of diastolic abnormalities and in monitoring therapeutic progress in a number of similar syndromes.[10,18,21,26]

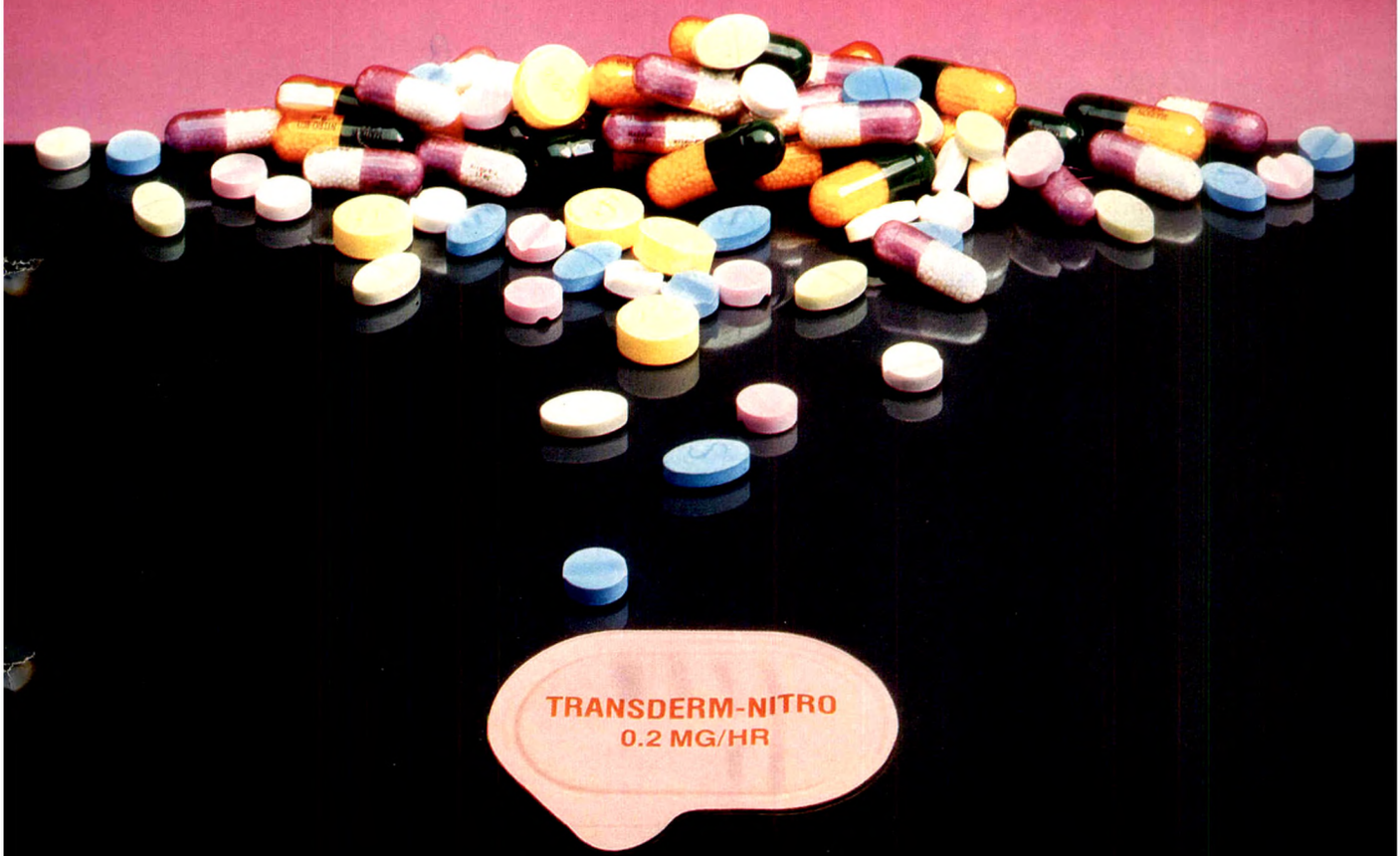
Mechanisms for the effect of verapamil: Possible mechanisms for the effect of verapamil in this study include altered hemodynamics, reversal of subclinical ischemic processes and altered cellular calcium metabolism. Only the first of these merits comment; the others lie outside of the scope of the present data. Modification of heart rate, afterload and preload all may serve to alter left ventricular filling.[27] With verapamil, peak filling rate increased significantly despite a decrease in heart rate. Because peak filling rate[28] and isovolumic relaxation time[29] usually vary directly with the heart rate, this suggests that the improvement in CHF and ventricular filling was not mediated by heart rate. Change in systolic blood pressure resulting in altered afterload probably did not contribute to this effect, because this parameter remained constant. Systemic vascular resistance was not measured; however, other invasive studies suggest that calcium antagonists do not act to reduce left ventricular end-diastolic pressure purely through afterload reduction.[30] Changes in preload cannot be confidently assessed, in that left ventricular filling pressures and echocardiographic dimensions were not measured. A direct effect on myocardium permitting improved diastolic filling may be considered. Further mechanistic studies in this area, especially those that address subcellular mechanisms, are clearly needed. Based on the data in this study, patients with CHF may be classified noninvasively by ejection fraction for appropriate pharmacotherapy. When impaired diastolic filling occurs with normal systolic performance, a trial of verapamil may be considered.

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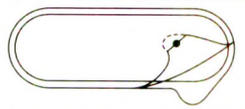
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BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE
This drug product has been conditionally approved by the FDA for the prevention of angina pectoris due to coronary artery disease. Tolerance to the antianginal effects of nitrates (measured by exercise stress testing) has been shown to be a major factor limiting efficacy when transdermal nitrates are used continuously for longer than 12 hours each day. The development of tolerance can be altered (prevented or attenuated) by use of a noncontinuous (intermittent) dosing schedule with a nitrate-free interval of 10-12 hours.

Controlled clinical trial data suggest that the intermittent use of nitrates is associated with decreased exercise tolerance, in comparison to placebo, during the last part of the nitrate-free interval; the clinical relevance of this observation is unknown, but the possibility of increased frequency or severity of angina during the nitrate-free interval should be considered. Further investigations of the tolerance phenomenon and best regimen are ongoing. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS
Allergic reactions to organic nitrates are extremely rare, but they do occur. Nitroglycerin is contraindicated in patients who are allergic to it. Allergy to the adhesives used in nitroglycerin patches has also been reported, and it similarly constitutes a contraindication to the use of this product.

WARNINGS
The benefits of transdermal nitroglycerin in patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use nitroglycerin in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia.

A cardioverter/defibrillator should not be discharged through a paddle electrode that overlies a Transderm-Nitro patch. The arcing that may be seen in this situation is harmless in itself, but it may be associated with local current concentration that can cause damage to the paddles and burns to the patient.

PRECAUTIONS
General
Severe hypotension, particularly with upright posture, may occur with even small doses of nitroglycerin. This drug should therefore be used with caution in patients who may be volume depleted or who, for whatever reason, are already hypotensive. Hypotension induced by nitroglycerin may be accompanied by paradoxical bradycardia and increased angina pectoris.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

As tolerance to other forms of nitroglycerin develops, the effect of sublingual nitroglycerin on exercise tolerance, although still observable, is somewhat blunted.

In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. Chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers, demonstrating the existence of true physical dependence.

Several clinical trials in patients with angina pectoris have evaluated nitroglycerin regimens which incorporated a 10-12 hour nitrate-free interval. In some of these trials, an increase in the frequency of anginal attacks during the nitrate-free interval was observed in a small number of patients. In one trial, patients demonstrated decreased exercise tolerance at the end of the nitrate-free interval. Hemodynamic rebound has been observed only rarely; on the other hand, few studies were so designed that rebound, if it had occurred, would have been detected. The importance of these observations to the routine, clinical use of transdermal nitroglycerin is unknown.

Information for Patients
Daily headaches sometimes accompany treatment with nitroglycerin. In patients who get these headaches, the headaches may be a marker of the activity of the drug. Patients should resist the temptation to avoid headaches by altering the schedule of their treatment with nitroglycerin, since loss of headache may be associated with simultaneous loss of antianginal efficacy.

Treatment with nitroglycerin may be associated with lightheadedness on standing, especially just after rising from a recumbent or seated position. This effect may be more frequent in patients who have also consumed alcohol.

After normal use, there is enough residual nitroglycerin in discarded patches that they are a potential hazard to children and pets.

A patient leaflet is supplied with the systems.

Drug Interactions
The vasodilating effects of nitroglycerin may be additive with those of other vasodilators. Alcohol, in particular, has been found to exhibit additive effects of this variety.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term animal studies have examined the carcinogenic or mutagenic potential of nitroglycerin. Nitroglycerin's effect upon reproductive capacity is similarly unknown.

Pregnancy Category C
Animal reproduction studies have not been conducted with nitroglycerin. It is also not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. Nitroglycerin should be given to a pregnant woman only if clearly needed.

Nursing Mothers
It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when nitroglycerin is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Adverse reactions to nitroglycerin are generally dose-related, and almost all of these reactions are the result of nitroglycerin's activity as a vasodilator. Headache, which may be severe, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses. Transient episodes of lightheadedness, occasionally related to blood pressure changes, may also occur. Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation of therapy. Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon.

Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients. Methemoglobinemia is so infrequent at these doses that further discussion of its diagnosis and treatment is deferred (see Overdosage).

Application-site irritation may occur but is rarely severe.

In two placebo-controlled trials of intermittent therapy with nitroglycerin patches at 0.2 to 0.8 mg/hr, the most frequent adverse reactions among 307 subjects were as follows:

	Placebo	Patch
Headache	18%	63%
Lightheadedness	4%	6%
Hypotension, and/or syncope	0%	4%
Increased angina	2%	2%

OVERDOSAGE
Hemodynamic Effects
The ill effects of nitroglycerin overdose are generally the result of nitroglycerin's capacity to induce vasodilatation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial pressure, with any or all of persistent throbbing headache, confusion, and moderate fever; vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially in the upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures; and death.

Laboratory determinations of serum levels of nitroglycerin and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of nitroglycerin overdose.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of nitroglycerin and its active metabolites. Similarly, it is not known which, if any, of these substances can usefully be removed from the body by hemodialysis.

No specific antagonist to the vasodilator effects of nitroglycerin is known, and no intervention has been subject to controlled study as a therapy of nitroglycerin overdose. Because the hypotension associated with nitroglycerin overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward an increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary.

The use of epinephrine or other arterial vasoconstrictors in this setting is likely to do more harm than good.

In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of nitroglycerin overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

Methemoglobinemia
Nitrate ions liberated during metabolism of nitroglycerin can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b_5 reductase activity, however, and even assuming that the nitrate moieties of nitroglycerin are quantitatively applied to oxidation of hemoglobin, about 1 mg/kg of nitroglycerin should be required before any of these patients manifests clinically significant (≥ 10%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of nitroglycerin. In one study in which 36 patients received 2-4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr, the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo.

Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible.

Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO_2. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air.

When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1-2 mg/kg intravenously.

DOSAGE AND ADMINISTRATION
The suggested starting dose is between 0.2 mg/hr*, and 0.4 mg/hr*. Doses between 0.4 mg/hr* and 0.8 mg/hr* have shown continued effectiveness for 10-12 hours daily for at least one month (the longest period studied) of intermittent administration. Although the minimum nitrate-free interval has not been defined, data show that a nitrate-free interval of 10-12 hours is sufficient (see INDICATIONS AND USAGE). Thus, an appropriate dosing schedule for nitroglycerin patches would include a daily patch-on period of 12-14 hours and a daily patch-off period of 10-12 hours.

Although some well-controlled clinical trials using exercise tolerance testing have shown maintenance of effectiveness when patches are worn continuously, the large majority of such controlled trials have shown the development of tolerance (i.e., complete loss of effect) within the first 24 hours after therapy was initiated. Dose adjustment, even to levels much higher than generally used, did not restore efficacy.

PATIENT INSTRUCTIONS FOR APPLICATION OF SYSTEM
A patient leaflet is supplied with each carton.

HOW SUPPLIED

Transderm-Nitro System*	Total Nitroglycerin in System	System Size	Carton Size	
0.1 mg/hr	12.5 mg	5 cm²	30 Systems	NDC 57267-902-26
			**30 Systems	NDC 57267-902-42
			**100 Systems	NDC 57267-902-30
0.2 mg/hr	25 mg	10 cm²	30 Systems	NDC 57267-905-26
			**30 Systems	NDC 57267-905-42
			**100 Systems	NDC 57267-905-30
0.4 mg/hr	50 mg	20 cm²	30 Systems	NDC 57267-910-26
			**30 Systems	NDC 57267-910-42
			**100 Systems	NDC 57267-910-30
0.6 mg/hr	75 mg	30 cm²	30 Systems	NDC 57267-915-26
			**30 Systems	NDC 57267-915-42
			**100 Systems	NDC 57267-915-30

**Institutional Pack

*Rated release in vivo. Release rates were formerly described in terms of drug delivered per 24 hours. In these terms, the supplied Transderm-Nitro systems would be rated at 2.5 mg/24 hr (0.1 mg/hr), 5 mg/24 hr (0.2 mg/hr), 10 mg/24 hr (0.4 mg/hr), and 15 mg/24 hr (0.6 mg/hr).

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References:
1 Brady EM, Gold OG, Rosenbach HJ. Antianginal efficacy of transdermal nitroglycerin and oral nitrates: The ACTION Study. *Cardiovasc Rev Rep*. October 1988: 40-44.

Changes in Circulating Norepinephrine with Hemofiltration in Advanced Congestive Heart Failure

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In congestive heart failure (CHF), hemofiltration is associated with an obvious decrease in circulating norepinephrine. This method was used for investigating the mechanisms whereby plasma norepinephrine is increased in chronic CHF. In 23 cases of advanced CHF, hemofiltration (2,983 ± 1,228 ml) lowered plasma norepinephrine by 515 ± 444 pg/ml. This effect was prompt, persisted or became greater in the next 24 hours. It was not associated with significant changes in cardiac output, aortic pressure or systemic vascular resistance. It did not appear to depend on variations in parameters related to the sympathetic activity, such as plasma renin, right atrial, wedge pulmonary artery and renal perfusion pressures, and was independent of duration and amount of hemofiltration. These observations did not support the concept that the norepinephrine decrease was the main consequence of a neural sympathetic inhibition. Hemofiltration increased diuresis by 606 ± 415 ml; changes were prompt and correlated inversely ($r = -0.7$; $p < 0.01$) with those in plasma norepinephrine. The same unknown mechanism of the increased urinary output might potentiate the norepinephrine removal from the blood by the kidney, or hemofiltration and the augmented diuresis might result in a regression of congestion of lungs and kidneys, leading to an improved extraction of norepinephrine.

In CHF, a relation may exist between fluid retention and norepinephrine and in advanced stages, circulating norepinephrine, although strikingly increased, is devoid of important cardiovascular effects. At these stages, plasma norepinephrine is probably unreliable as an index of the sympathetic neural activity.

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The repeated observation that the sympathetic neurotransmitter norepinephrine is present at increased concentration in plasma of patients with congestive heart failure (CHF) has led to the consensus that sympathetic nervous overactivity is important in the pathophysiology of the syndrome.[1] The prognostic significance of the norepinephrine plasma levels in cardiac failure has also been emphasized.[2]

It is documented that the increase in circulating norepinephrine is caused by an interaction between increased spillover and decreased clearance[3,4] both at rest and during stressful situations.[5] Several basic points remain unsettled regarding the signal that initiates the heightened sympathetic drive,[3] the mechanisms for the decreased clearance of norepinephrine[5] and the hemodynamic correlates of the circulating norepinephrine.[6–11]

Hemofiltration allows subtraction of plasma water[11,12] and, in patients with CHF, has been shown to promote prompt decrease of the circulating sympathetic neurotransmitter, along with an increase in urinary output and relief of organ congestion.[13,14] Thanks to these adjustments, hemofiltration may be viewed as a nonpharmacologic means by which the concentration of circulating norepinephrine in patients with CHF may be subjected to large, prompt and persistent modifications.

METHODS

Patients: Twenty-three patients (16 men and 7 women, whose age ranged between 42 and 77 years, average 63) were involved and gave their written consent to the study after receiving detailed information regarding the procedures, the possible clinical benefits and the investigative purposes. The protocol was approved by the ethical committee of the Institute of Cardiology, University of Milan. All patients were breathless on moderate exertion or at rest (New York Heart Association class III to IV), with cardiomegaly, dependent edema and radiologic evidence of lung congestion; 6 also had pleural effusion (Table I). Subjects were treated with a constant dose of furosemide and digoxin in the hospital for several days before study. Digoxin and furosemide were continued at the same doses during the study and were administered ≥16 hours before each set of measurements. Vasodilators, including converting enzyme inhibitors, or inotropic drugs other than digitalis, had previously been administered to several

TABLE I Clinical Characteristics in 23 Patients

Patient No.	Age (yr) & Sex	Etiology	NYHA Class	Clinical Data		Prior Therapy					Current Therapy	
				PL EFF	PERIPH ED	DIG	ACEI	S VAS	INOT	LAN	DIG (mg)	FUR (mg)
1	42 M	CAD	IV	No	Yes	Yes	Yes*	No	No	Yes†	0.25	160
2	48 M	CAD	IV	No	Yes	Yes	Yes*	Yes	No	Yes†	0.25	500
3	58 M	CAD	IV	Yes	Yes	Yes	No	Yes	Yes	Yes†	0.25	700
4	59 M	CAD	III	Yes	Yes	Yes	Yes*	Yes	Yes	No	0.25	250
5	64 M	CAD	IV	No	Yes	Yes	No	No	No	Yes†	0.25	120
6	65 M	CAD	IV	No	Yes	Yes	No	Yes	Yes	Yes†	0.50	440
7	66 M	CAD	IV	No	Yes	Yes	Yes*	No	No	Yes†	0.25	125
8	67 F	CAD	III	No	Yes	Yes	No	No	Yes	Yes†	0.25	120
9	68 F	CAD	IV	No	Yes	Yes	No	Yes	No	Yes†	0.25	200
10	68 M	CAD	IV	No	Yes	Yes	No	No	Yes	Yes†	0.50	120
11	70 F	CAD	IV	No	Yes	Yes	No	No	Yes	Yes†	0.50	200
12	73 F	CAD	IV	No	Yes	Yes	Yes*	No	Yes	Yes†	0.50	180
13	77 M	CAD	IV	No	Yes	Yes	No	Yes	No	Yes†	0.125	100
14	47 M	IDC	IV	No	Yes	Yes	Yes*	No	No	Yes†	0.50	500
15	51 M	IDC	IV	No	Yes	Yes	No	Yes	Yes	No	0.50	375
16	57 M	IDC	III	No	Yes	Yes	Yes*	Yes	No	No	0.50	160
17	58 M	IDC	IV	No	Yes	Yes	No	Yes	Yes	Yes†	0.25	250
18	59 M	IDC	IV	Yes	Yes	Yes	Yes*	No	No	Yes†	0.50	160
19	64 F	IDC	IV	Yes	Yes	Yes	No	Yes	No	Yes†	0.25	125
20	70 F	IDC	III	Yes	Yes	Yes	No	Yes	No	Yes†	0.25	300
21	72 M	IDC	IV	No	Yes	Yes	No	Yes	No	Yes†	0.50	200
22	73 M	IDC	IV	No	Yes	Yes	No	No	Yes	Yes†	0.50	120
23	77 F	IDC	IV	Yes	Yes	Yes	No	Yes	Yes	Yes†	0.50	400

*Discontinued 4 days before study; † discontinued at least 48 hours before study.
ACEI = angiotensin-converting enzyme inhibitors; CAD = coronary artery disease; DIG = digoxin; FUR = furosemide; IDC = idiopathic dilated cardiomyopathy; INOT = inotropic compounds; LAN = long-acting nitrates; NYHA = New York Heart Association functional class; PERIPH ED = peripheral edema; PL EFF = pleural effusion; S VAS = systemic vasodilator.

subjects and were withheld for ≥4 days before the study. The amount of dietary sodium did not exceed 50 mEq and the mean dose of furosemide was 253 mg/24 hours (range 100 to 700). Diuresis ranged between 50 and 2,650 ml/24 hours and averaged 967 ml in the 24 hours preceding the hemofiltration. For the group, mean (± standard deviation) values of blood urea nitrogen (mg/dl) and serum creatinine concentration (mg/dl) were 125 (± 75) and 2.29 (± 1.17), respectively.

Humoral measurements: Plasma norepinephrine was determined by high-performance liquid chromatography.[15] Plasma-renin activity was measured by radioimmunoassay of angiotensin I.[16] These tests were performed on arterial blood withdrawn from the brachial artery.[17] Humoral measurements in all samples from a single patient were obtained in the same assay. The intraassay variations in our laboratory are 4% for plasma norepinephrine and 6% for renin. The normal values (±

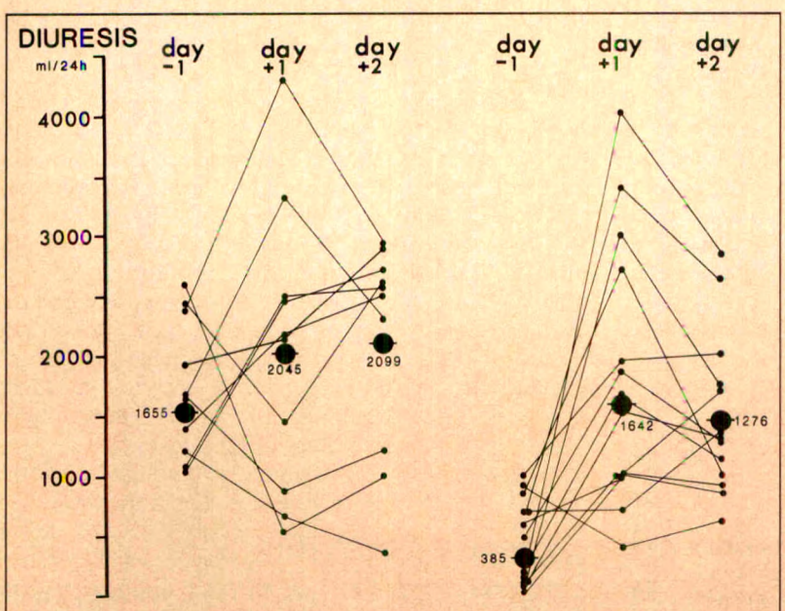


FIGURE 1. Twenty-four hour urinary output at day −1, day +1 and day +2 in 10 patients whose diuresis was >1,000 ml (*left*) and in 13 patients whose diuresis was <1,000 ml in 24 hours (*right*). *Large symbols* indicate averages.

TABLE II Hemodynamics

Hemodynamic Parameters	Day −1	Day 0	Day +1
Heart rate (beats/min)	90 ± 13	88 ± 13	89 ± 14
Mean systemic arterial pressure (mm Hg)	91 ± 20	90 ± 18	88 ± 16
Mean pulmonary arterial pressure (mm Hg)	44 ± 10	34 ± 7*	35 ± 11*
Mean pulmonary wedge pressure (mm Hg)	31 ± 7	20 ± 6†	22 ± 8†
Mean right atrial pressure (mm Hg)	19 ± 6	8 ± 6†	12 ± 7*
Cardiac index (liters/min/m^2)	2.3 ± 0.8	2.2 ± 0.7	2.5 ± 1
Left ventricular stroke work index (g·m/m^2)	41 ± 21	41 ± 20	43 ± 22
Systemic vascular resistance (dynes·s·cm^{-5})	1,488 ± 579	1,682 ± 669	1,404 ± 492
Pulmonary vascular resistance (dynes·s·cm^{-5})	302 ± 195	334 ± 252	301 ± 239
Renal perfusion pressure (mm Hg)	72 ± 22	82 ± 19*	76 ± 18
Ultrafiltrate (ml)		2,983 ± 1,228	

Data are mean ± standard deviation.
Differences from baseline (day −1) significant at * $p < 0.01$ and † $p < 0.001$, respectively.

standard deviation) in the supine position in our laboratory are as follows: plasma norepinephrine, 167 ± 58 pg/ml; and plasma renin activity, 2.3 ± 0.7 ng/ml/hr.

Hemodynamic measurements: For the invasive procedures, patients were admitted to the intensive care unit. The hemodynamic evaluations were obtained through a number 8 flow-directed triple-lumen thermodilution catheter inserted percutaneously into an antecubital or subclavian vein and advanced to the pulmonary artery, or, when necessary, to the wedge position. The proximal port of the catheter was used for the pressure measurements in the right atrium. Systemic arterial pressure was derived from a short catheter introduced into a brachial artery. Arterial and venous catheters were maintained in place for 3 consecutive days. Pressures were determined with Hewlett-Packard (Waltham, Massachusetts) strain-gauge transducers (model 1286B) and recorded on a Hewlett-Packard 8-channel recorder (model 1064C). Cardiac output was obtained by thermodilution through an Edwards (Santa Ana, California) cardiac output computer (9520A); measurements were made in triplicate at each period and the mean was taken as the representative value. From the ratio of the driving pressure through the systemic (mean arterial pressure minus mean right atrial pressure) and the pulmonary circuit (mean pulmonary arterial pressure minus mean wedge pulmonary pressure) and cardiac output, we calculated the systemic and pulmonary arteriolar resistance (dynes·s·cm^{-5}). The driving pressure through the systemic circuit was also taken as an index of the driving pressure through the kidneys.

Hemofiltration: The procedure has been described previously in more detail.[14] We used a D20SF Amicon (Danvers, Massachusetts) diafilter, which allows filtration of plasma water and solutes of <50,000 daltons. The filter was inserted into an external venous circuit by

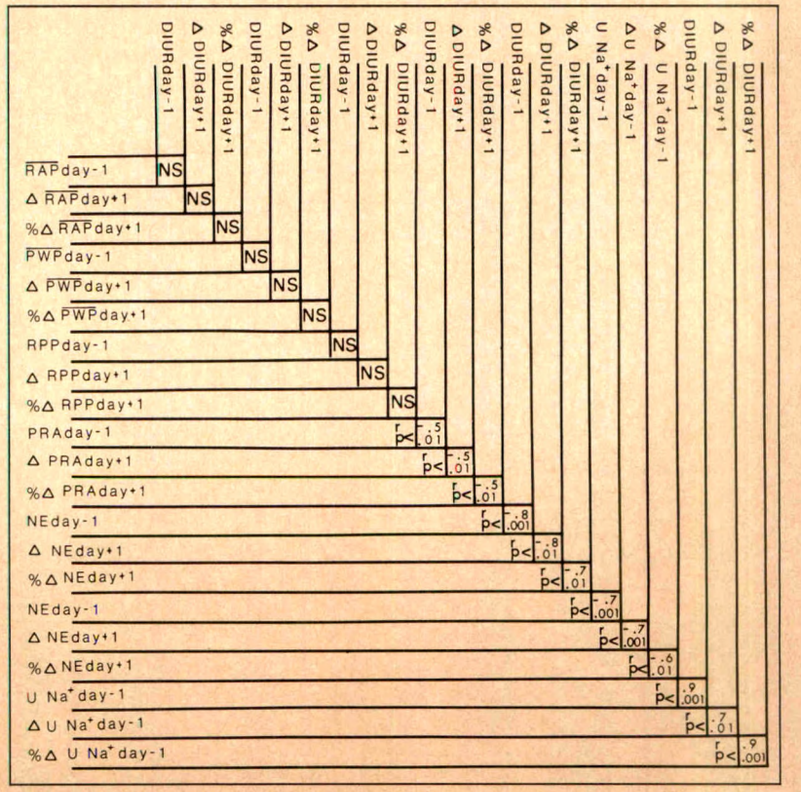


FIGURE 2. Correlations of urinary output on day −1 and its absolute and percent changes on day +1, with the corresponding values of hemodynamic and humoral parameters possibly involved in the regulation of sodium and water excretion. NE = plasma norepinephrine concentration; NS = not significant; PRA = plasma renin activity; PWP = mean pulmonary artery wedge pressure: RAP = mean right atrial pressure; RPP = renal perfusion pressure; U Na^+ = 24-hour urinary sodium excretion.

TABLE III Norepinephrine, Plasma Renin Activity, Sodium, Diuresis and Renal Function

Parameters	Day −1	Day 0	Day +1	Day +2 (n)
Plasma norepinephrine (pg/ml)	2,322 ± 1,440	1,807 ± 993*	1,439 ± 613†	1,209 ± 554* (17)
Plasma renin activity (ng/ml/hour)	21.8 ± 19.5	28.2 ± 16.9*	18.6 ± 17.1	15.7 ± 13.3 (18)
Diuresis (ml/24 hours)	967 ± 905	1,573 ± 925†	1,934 ± 1,034†	1,582 ± 755† (23)
Urinary sodium excretion (mEq/24 hours)	56 ± 51	108 ± 44†	124 ± 54†	119 ± 39* (19)
Serum sodium concentration (mEq/liter)	139 ± 10	145 ± 13	141 ± 12	143 ± 10 (21)
Blood urea concentration (mg/dl)	124 ± 77	138 ± 84	131 ± 75	126 ± 55 (21)
Serum creatinine concentration (mg/dl)	2.3 ± 1.1	3.5 ± 2.6	2.4 ± 1.5	3.2 ± 2.4 (21)
Body weight (kg)	74 ± 22	71 ± 20	68 ± 21	67 ± 20 (23)

Data are mean ± standard deviation.
Differences from baseline (day −1) significant at * $p < 0.01$; and † $p < 0.001$, respectively.

connecting the inlet port to a high-flow dialysis catheter introduced into the right femoral vein and the outlet port to a hemodialysis 14G Angiocath Deseret inserted into an antecubital vein. The flow through the circuit was driven by a Gambro System (Lund, Sweden) AK10 peristaltic pump (model BMM 10-1K) regulated to remove ultrafiltrate at a rate of 600 ml/hour.

Ultrafiltration was continued until the mean right atrial pressure, which was elevated in all patients before the procedure (mean 19 mm Hg), lowered to between 4 and 8 mm Hg or until hematocrit exceeded 50%. The amount of fluid removed ranged between 1,000 and 4,980 ml (average 2,983). The filtering circuit was kept in place just for the duration of the procedure.

Study protocol: Simultaneous hemodynamic and humoral measurements were taken on the following 3 consecutive days: day −1 (before hemofiltration); day 0 (hemofiltration); and day +1 (after hemofiltration). Serum catecholamine and renin tests were also available on a subsequent day (day +2) only in a reduced number of patients—those whose arterial catheter was kept inserted.

Although previous studies have shown that the plasma norepinephrine concentration is stable when measured on successive days in hospitalized patients with heart failure and is not markedly influenced by invasive hemodynamic procedures,[17] care was taken to avoid an interference of the surroundings or instrumentation. Measurements were performed in an air conditioned room at 22°C, after an overnight fast. Tea, coffee, cigarettes and alcohol were not taken during the 12 hours preceding each set of measurements. The achievement of a basal condition was assured by stability (<10% variation) in heart rate, blood pressure, pulmonary artery wedge pressure and cardiac output, for at least 1 hour before the beginning of the circulatory records and blood sampling for the humoral tests. On the morning of day 0, after the baseline measurements, the venous external circuit was settled and ultrafiltration was started. The hemodynamic parameters were assessed every 30 minutes during hemofiltration. The baseline circulatory and humoral values on day 0 (data not shown) were quite similar to those on day −1. Those obtained at the end of the procedure were identified as day 0 values. The following variables, from day −1 to day +2, were also measured daily: body weight; urinary output; sodium serum concentration and urinary excretion; blood urea nitrogen; and serum creatinine concentrations.

Statistical method: A 1-way analysis of variance was used to evaluate the day-to-day variability of the various plasma, urinary and circulatory variables. Analysis by 2 variables linear regression was used to compare humoral variables and hemodynamics in the base-

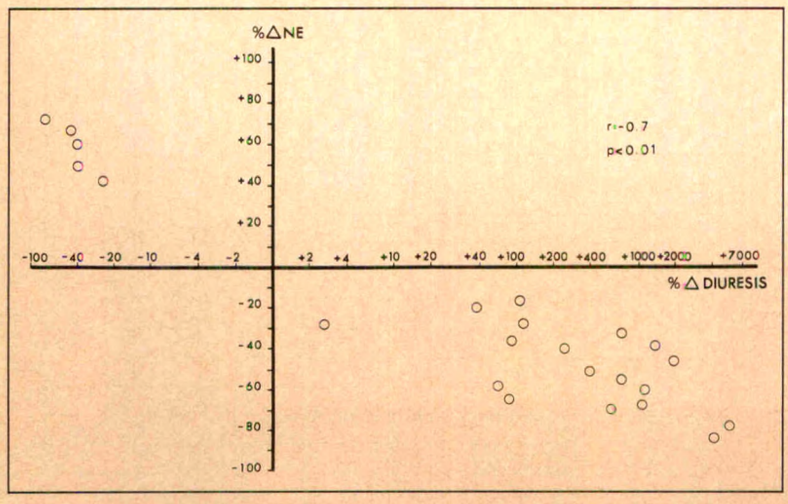


FIGURE 3. Correlation between percent changes in plasma norepinephrine on day +1 and variations in the 24-hour urinary volume. ΔNE = change in plasma norepinephrine concentration.

line and their respective changes at different times after hemofiltration. Data are expressed as mean ± standard deviation. A p value <0.01 was considered statistically significant.

RESULTS

Control measurements and their changes with hemofiltration: HEMODYNAMICS: The elevated filling pressures of the 2 ventricles and the reduced cardiac and stroke indexes document that cardiac function in these patients was severely compromised (Table II). As reported previously,[14] subtraction of plasma water (average 2,983 ml) was not associated with changes in cardiac index and left ventricular stroke work, even though the mean right atrial and wedge pulmonary pressures were greatly and significantly lowered. Heart rate, aortic pressure and systemic vascular resistance were not responsive to the procedure. These hemodynamic adjustments persisted 24 hours later. The renal perfusion pressure was significantly raised soon after hemofiltration and not on day +1. Clinical improvement with hemofiltration was unquestionable, as reflected by resolution of peripheral edema, relief of dyspnea, of lung congestion and of pleural effusion. Along with these hemodynamic and clinical changes hemofiltration caused a number of humoral changes.

SODIUM, DIURESIS AND RENAL FUNCTION: In the control condition, the 24-hour urinary output averaged 967 ml and increased by 606, 967 and 616 ml on day 0, +1 and +2, respectively (Table III). Daily sodium excretion, from the control value of 56 mEq, was also significantly raised by 52, 68 and 63 mEq on days 0, +1 and +2. Blood urea nitrogen and serum creatinine concentrations were 124 mg/dl and 2.3 mg/dl in the baseline condition and did not vary significantly after hemofiltration; serum sodium concentration was slightly and persistently raised after the procedure.

Figure 1 shows individual values of diuresis at the various steps. Patients with 24-hour urinary volume >1,000 ml before hemofiltration (left) were separated from those whose urinary output was <1,000 ml (right). Subtraction of plasma water activated diuresis regardless of the 24-hour urinary output, this effect being evident when the output was normal as well as when it was depressed to levels as low as 100 ml or even less. The diuretic effect was maximal soon after hemofiltration and persisted in the subsequent 24 hours. Hemofiltration elicited an oliguric response in some cases (5 cases).

NOREPINEPHRINE AND RENIN ACTIVITY: Plasma norepinephrine and renin activity were substantially raised in the control state in these patients (Table III). Those with lower urinary output had a particularly marked humoral activation. Norepinephrine (pg/ml) ranged from 486 to 5,480 on day −1, from 388 to 3,788 on day 0, from 316 to 3,278 on day +1 and from 604 to 3,166 on day +2. Plasma renin activity (ng/ml/hr) ranged from 0.70 to 80, from 1.50 to 66, from 0.28 to 41 and from 0.28 to 40 at the corresponding periods. Plasma norepinephrine and renin moved to an opposite direction on day 0 and to a similar direction on day +1 and +2.

Correlations with water and sodium excretion: We correlated the urinary output on day −1 and its abso-

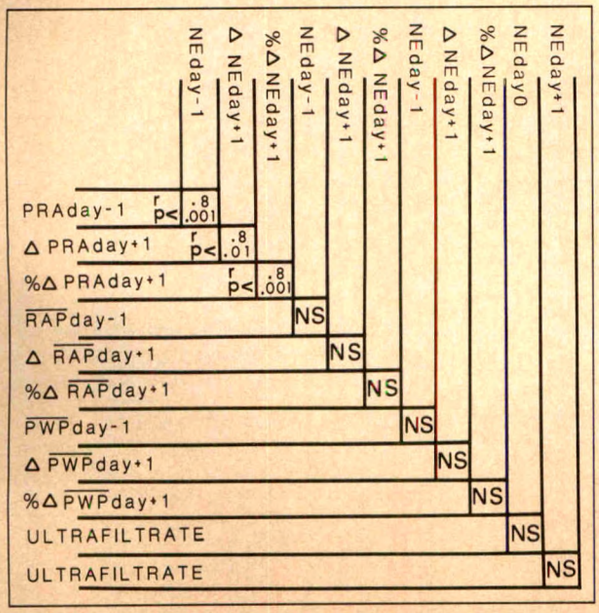


FIGURE 4. Correlations of plasma norepinephrine concentration on day −1 and its absolute and percent variations on day +1, with the corresponding values of parameters possibly involved in the regulation of circulating norepinephrine. Abbreviations as in Figure 2.

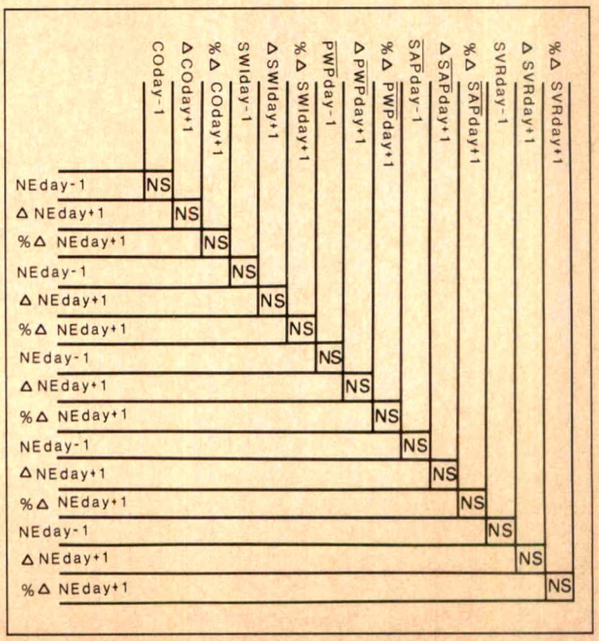


FIGURE 5. Correlations of norepinephrine plasma concentration on day −1 and its absolute and percent changes on day +1, with corresponding values of cardiac and systemic hemodynamic parameters. CO = cardiac output; NE = norepinephrine plasma concentration; PWP = mean pulmonary artery wedge pressure; SAP = mean systemic arterial pressure; SVR = systemic vascular resistance; SWI = left ventricular stroke work index.

lute and percent variations on day +1 with the corresponding values of humoral and hemodynamic parameters possibly involved in the regulation of sodium and water excretion (Figures 2 and 3). These parameters were the following: 24-hour urinary sodium excretion,[18] right atrial pressure,[19,20] pulmonary artery wedge pressure,[21,22] renal perfusion pressure, plasma renin activity[23] and plasma norepinephrine concentration.[24] Correlations were significant between diuresis and urinary sodium excretion, plasma renin activity and plasma norepinephrine concentration, and between their absolute and percent changes on day +1. There was also a significant correlation between day −1 plasma norepinephrine concentration and urinary sodium excretion, as well as between their respective changes on day +1.

Figure 3 shows the inverse relation existing between percent changes in plasma norepinephrine on day +1 and the equivalent variations in the 24-hour urinary volume; these changes were greater in the oliguric population and patients whose urinary output was diminished by hemofiltration (5 cases); all had an increase of the circulating sympathetic neurotransmitter.

Correlations with plasma norepinephrine: The circulating norepinephrine on day −1 and the absolute and percent variations on day +1 were correlated with the corresponding values of plasma renin activity,[24] right atrial[10,17] and wedge pulmonary pressures (Figure 4). These variables were chosen because they are potentially related to the overactivity of the sympathetic nervous system in cardiac failure. Correlations were significant only between norepinephrine and renin and between their respective changes. The amount of water filtered did not correlate with the circulating levels of norepinephrine at the end of the procedure (day 0), as well as 24 hours later (day +1).

Norepinephrine and cardiovascular function: Cardiac output, left ventricular stroke work index, mean pulmonary artery wedge pressure, systemic arterial pressure and vascular resistance in the control state, as well as their absolute and percent changes on day +1, did not correlate with the corresponding plasma levels of the sympathetic neurotransmitter (Figures 5 and 6). Norepinephrine in plasma under most circumstances is devoid of metabolic and cardiovascular effect; in normal persons, the plasma concentration typically must increase at least fivefold (>1,800 pg/ml) to reach threshold for such an effect.[25] Because of this, for the analysis of a possible relation between changes in hemodynamic variables and in plasma norepinephrine concentration, we divided the patients in 2 groups, taking a norepinephrine plasma concentration of 1,800 pg/ml as the cutoff value for discriminating those in whom norepinephrine might represent a circulating hormone (Figure 6, right), The percent circulatory variations were small in both groups and, even though systemic vascular resistance decreased more in those patients whose plasma norepinephrine was as high as to act as a circulating hormone, no group differences reached statistical significance.

DISCUSSION

Although a potentiation of the urinary output after hemofiltration has been observed repeatedly,[13,14,26] the mechanism is unknown. In this study, the diuretic response was inversely related to the urinary output before the procedure and the excretion of salt and water increased greatly even in cases of severe oliguria. With this, there was a substantial decrease of circulating norepinephrine. It might be speculated that the decrease in the circulating neurotransmitter, as such or as a reflection of weaker renal sympathetic firing, augmented the urinary output.[27] This, however, implies that adrenergic withdrawal was able to potentiate diuresis by an average of 1,300 ml in the group of patients whose daily diuresis before hemofiltration was <1,000 ml, and that the sympathetic system is the major culprit of fluid retention in CHF. Because of these considerations, reduction in circulating norepinephrine probably is not the

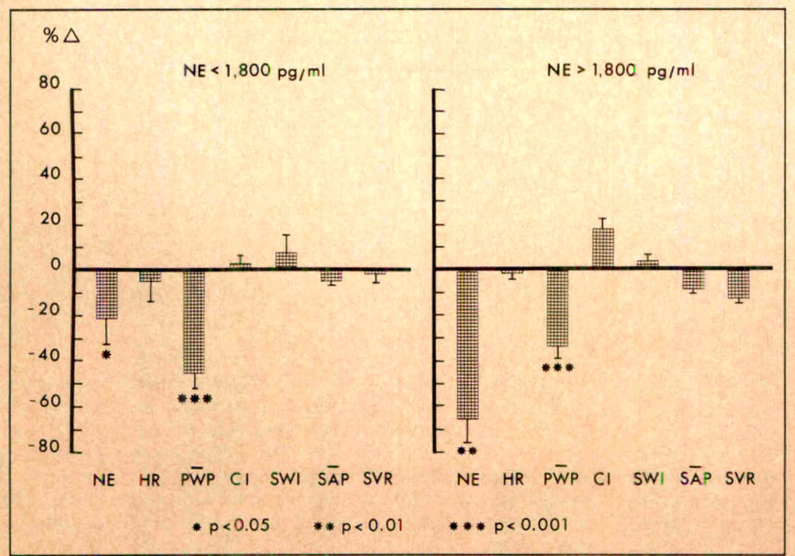


FIGURE 6. Percent variations on day +1 of plasma norepinephrine concentration and hemodynamic variables in patients whose circulating norepinephrine was < (*left*) or > (*right*) 1,800 pg/ml (mean ± standard error of the mean). CI = cardiac index; HR = heart rate; NE = norepinephrine plasma concentration; PWP = mean pulmonary artery wedge pressure; SAP = mean systemic arterial pressure; SVR = systemic vascular resistance; SWI = left ventricular stroke work index.

main mechanism whereby hemofiltration potentiates salt and water excretion.

An important question is whether or not subtraction of water from plasma causes a neural sympathetic inhibition and the norepinephrine decrease is a consequence of it. The usual response to a reduction in extracellular volume is an increase and not a decline in sympathetic nerve firing.[27] Another significant point is the dissociation between the plasma levels of norepinephrine and function of the cardiovascular system: even a 66% decrease of norepinephrine (patients whose levels in the plasma were >1,800 pg/ml) was devoid of significant circulatory effects. Reasonably, results would be different if such changes were the consequence of a 66% inhibition of the neural sympathetic tone. These patterns also suggest that the elevation of the sympathetic neurotransmitter in chronic CHF does not contribute significantly to the hemodynamic abnormalities because, for some reason, it accumulates in excess relative to the amount required for activity at the level of adrenergic receptors.[28]

In the majority of cases, decrease of circulating norepinephrine was proportional to the potentiation of diuresis. In each of the 5 patients in whom hemofiltration resulted in a decrease of the 24-hour urinary volume, norepinephrine increased in the plasma. Changes were obvious as early as at completion of the filtration procedure regardless of the duration and the amount of fluid removed. It seems that there was a link between the 2 variables and that the coupling mechanisms were such as to come into action without delay. The renin-angiotensin system importantly influences sodium and water excretion and exerts a reciprocal positive feedback with the sympathetic nervous system.[29] Changes in renin showed a strong correlation with changes in urinary volume as well as with those in plasma norepinephrine on day +1. However, a hypothetical linking role of renin is contradicted by the opposite direction in which norepinephrine and renin moved on day 0.

The concentration of norepinephrine in the plasma is determined by the rates of both release of norepinephrine to plasma and removal of norepinephrine from plasma. Outflow of norepinephrine from the kidneys accounts for approximately 25% of the total spillover of norepinephrine to plasma in healthy subjects and the fractional extraction of norepinephrine by the kidneys ranges between 35 and 55%.[30] Studies in humans with CHF have proven that the kidneys are largely involved in raising the circulating norepinephrine, possibly in consequence of a disproportionate reduction in flow. Experiments in dogs[30] have documented that there is a flow dependence of norepinephrine clearance by the kidneys for any extent of flow reduction and for norepinephrine spillover at high degrees of flow reduction.[30] In our study, we recorded some improvement in the renal perfusion pressure after hemofiltration; however, lack of measurements of renal plasma flow is a limitation to our conclusion.

An alternative interpretation is advanced. Subtraction of water from the plasma with hemofiltration translates into reabsorption of a comparable amount of extravascular water,[16] resulting in regression of peripheral edema and organ congestion. This process may be maintained because of the raised diuresis and lead to a persistent enhancement of the norepinephrine removal from circulation by different organs. Relief of lung congestion has an important part in the improved fractional extraction, since lungs possess a high extraction rate of norepinephrine[30] and a blood flow that equals 100% of cardiac output.

In CHF, oliguria and organ congestion might be suggested as 2 of the factors that alter the balance between norepinephrine overflow to plasma and total norepinephrine plasma clearance; elevated circulating levels of the neurotransmitter probably do not reflect the intensity of the neural firing.

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The most prescribed calcium channel blocker for hypertension[1] gets even better

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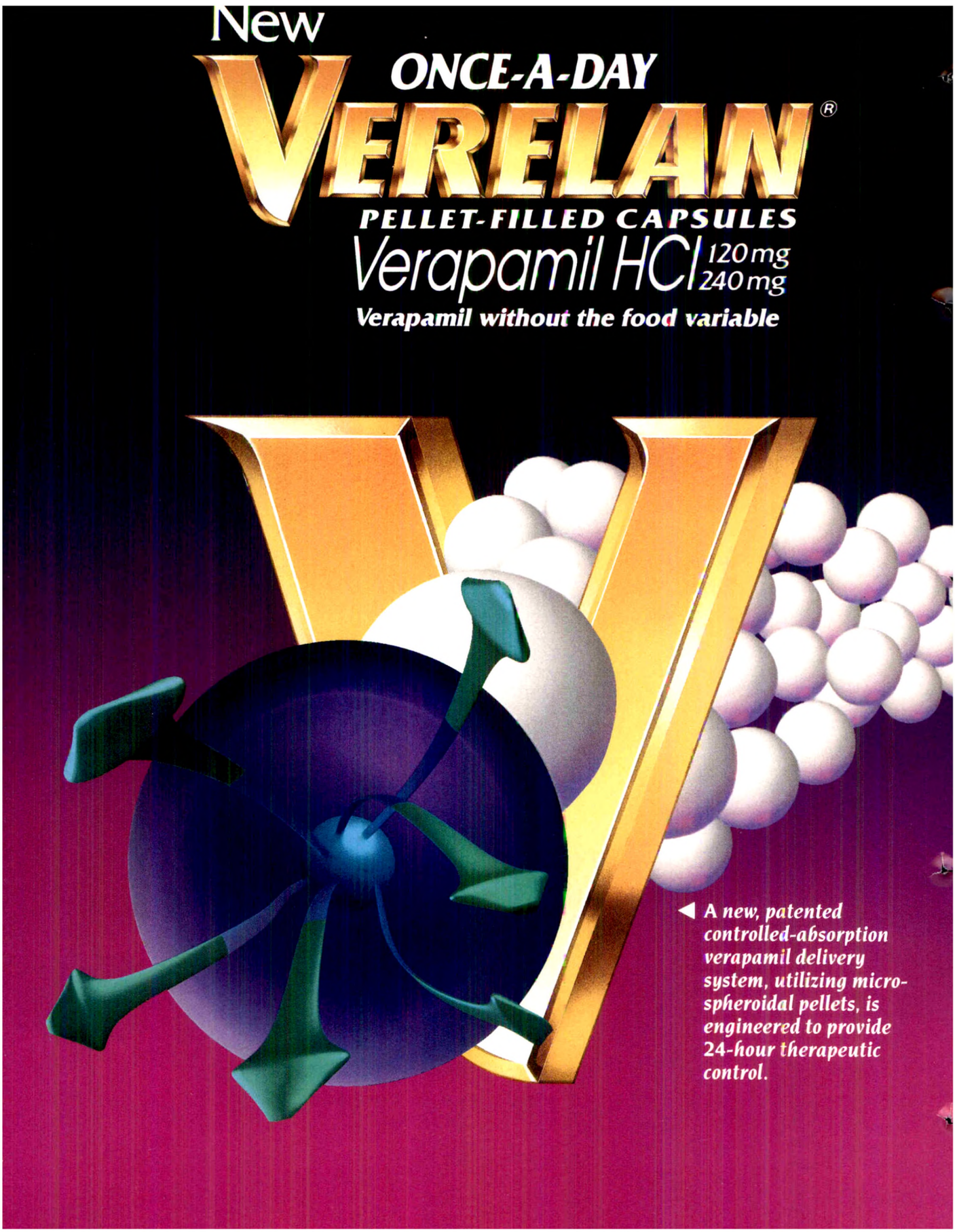
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*US Patent Number: 4,863,742

†Calan® SR (GD Searle & Co), Isoptin® SR (Knoll Pharmaceuticals).

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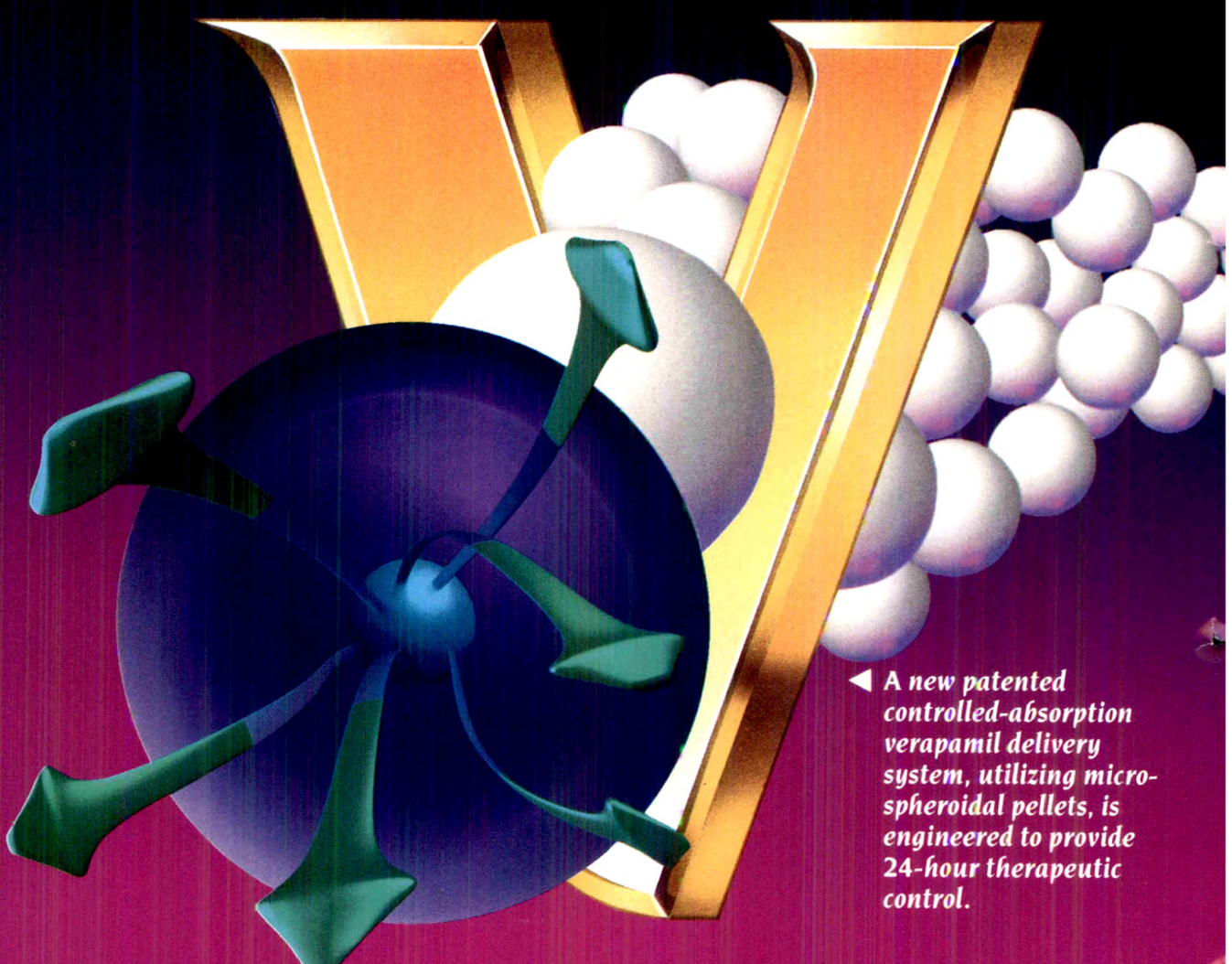
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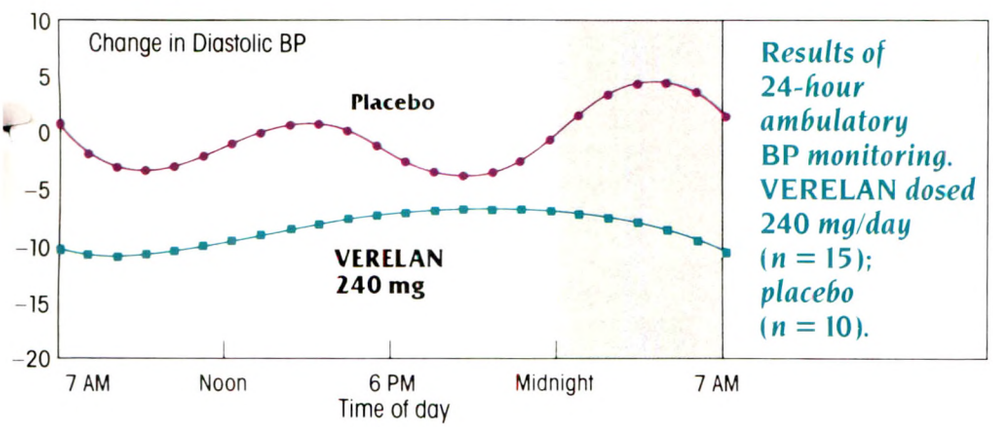


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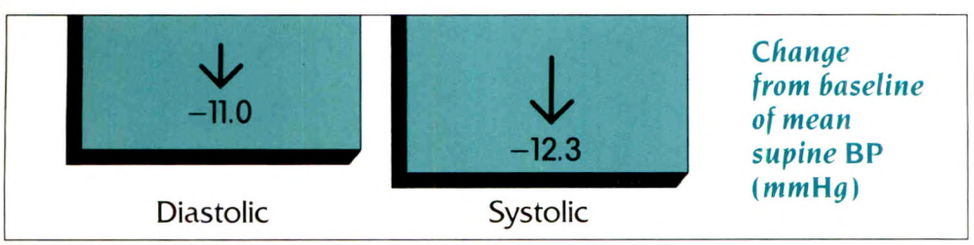
IN CASES STUDIED... AMBULATORY MONITORING DOCUMENTS MONOTHERAPY SUCCESS[3]

- Maintains control throughout the early morning hours, the period usually associated with greatest cardiovascular risk



Results of 24-hour ambulatory BP monitoring. VERELAN dosed 240 mg/day (n = 15); placebo (n = 10).

- Maintains 24-hour effectiveness in reducing elevated blood pressure—with one daily dose



Change from baseline of mean supine BP (mmHg)

Results of a 4-week, double-blind, placebo-controlled study. VERELAN dosed 240 mg/day (n = 27).[3,4]

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New

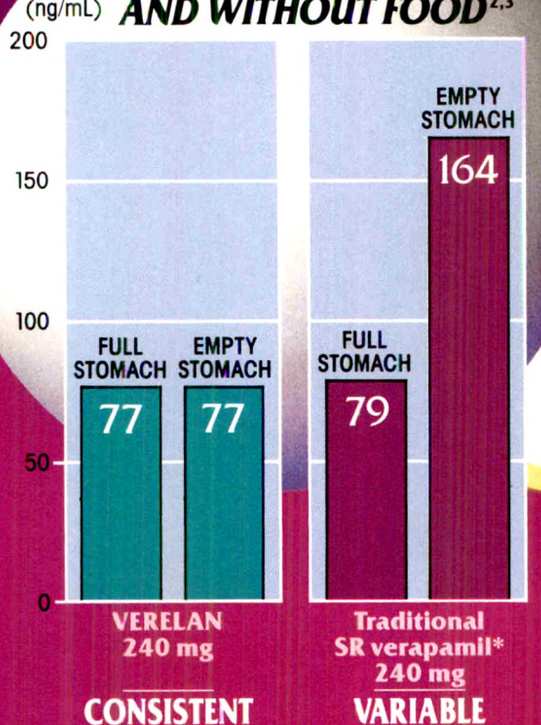
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PEAK VERAPAMIL BLOOD LEVELS WITH AND WITHOUT FOOD[2,3]



◀ ***Traditional SR verapamil* should not be taken on an empty stomach. Failure to take traditional SR verapamil with food may result in a two-fold variation in peak blood levels.***

With VERELAN, absorption is consistent—with and without food.

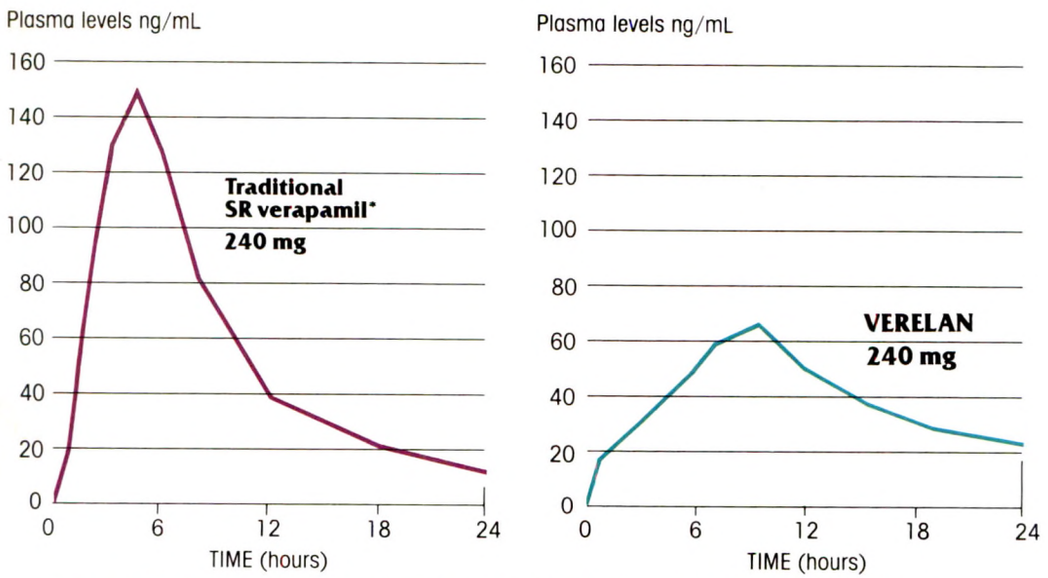
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VERELAN: Engineered for convenience

RELIABLE ABSORPTION WITH OR WITHOUT FOOD

- Patient lifestyles often make it impractical for regular dosing with full meals
- Patients may not be able to take traditional SR verapamil* on a full stomach as recommended[2]
- Controlled-absorption VERELAN can be taken with or without food, thus eliminating the variation in peak levels observed with traditional SR verapamil* therapy if taken on an empty stomach[2,3]

Smoother verapamil blood levels over 24 hours without food



Fasting blood level comparison from two individual fed/fasting studies[3]

- Constipation, which can be easily managed in most patients, is the most frequently reported side effect of verapamil

VERELAN is contraindicated in severe left ventricular dysfunction, hypotension, or cardiogenic shock, and sick sinus syndrome or second- or third-degree AV block.

Please see brief summary of Prescribing Information on next page.

ONCE-A-DAY VERELAN®



PELLET-FILLED CAPSULES

Verapamil HCl 120 mg 240 mg

Verapamil without the food variable



- New absorption profile
- Advanced convenience
- Advanced dosing simplicity

The usual dose is 240 mg once daily. If adequate response is not obtained, the dose may be titrated up to 360 mg or 480 mg once daily. VERELAN 120 mg is available for patients requiring lower dose verapamil therapy.

References: 1. Pharmaceutical Data Services, Alpha Data Services, December, 1989. 2. *Physicians' Desk Reference (PDR®)*; 44th ed. Oradell, NJ: Medical Economics Co Inc; 1990: 1117-1119 (Isoptin SR):2053-2056 (Calan SR). 3. Data on file, Lederle Laboratories, Pearl River, NY. 4. Bottini PB, Carr AA, Rhoades RE, Prisant LM, O'Brien DE. Dose response of a new once daily verapamil capsule confirmed by ambulatory blood pressure monitoring. Presented at the Fifth Scientific Meeting of the American Society of Hypertension; May 17-21, 1990; New York, NY. Abstract.

Brief Summary
VERELAN® Verapamil HCl
Sustained-Release Pellet-Filled Capsules

For complete Prescribing Information, consult package insert.

CLINICAL PHARMACOLOGY: Food does not affect the extent or rate of the controlled absorption of verapamil from the VERELAN capsule.

Atrioventricular block can occur in patients without preexisting condition defects (see **WARNINGS**).

Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil (see **WARNINGS**).

In patients with hepatic insufficiency, metabolism is delayed and elimination half-life prolonged up to 14 to 16 hours (see **PRECAUTIONS**), the volume of distribution is increased, and plasma clearance reduced to about 30% of normal.

CONTRAINDICATIONS: Severe LV dysfunction (see **WARNINGS**), hypotension (systolic pressure <90 mmHg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), second- or third-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), (see **WARNINGS**), hypersensitivity to verapamil.

WARNINGS: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction <30%) or moderate-to-severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta blocker. Control milder heart failure with optimum digitalization and/or diuretics before VERELAN is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported.

Several cases of hepatocellular injury have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving IV verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (second- and third-degree, 0.8%). Development of marked first-degree block or progression to second- or third-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, second-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

PRECAUTIONS: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Verapamil has been given concomitantly with short- and long-acting nitrates without any undesirable drug interactions. Interaction between cimetidine and chronically administered verapamil has not been studied. In healthy volunteers, clearance of verapamil was reduced or unchanged. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully.

Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. **Pregnancy Category C:** There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use. Safety and efficacy of verapamil in children below the age of 18 years have not been established.

ADVERSE REACTIONS: In clinical trials with 285 hypertensive patients on VERELAN *verapamil HCl sustained-release pellet-filled capsules* for more than 1 week, the following adverse reactions were reported: constipation (7.4%); headache (5.3%); dizziness (4.2%); lethargy (3.2%); dyspepsia (2.5%); rash (1.4%); ankle edema (1.4%); sleep disturbance (1.4%); myalgia (1.1%). In clinical trials of other formulations of verapamil HCl (N = 4,954), the following reactions have occurred at rates greater than 1.0%: constipation (7.3%); dizziness (3.3%); nausea (2.7%); hypotension (2.5%); edema (1.9%); headache (2.2%); rash (1.2%); CHF/pulmonary edema (1.8%); fatigue (1.7%); bradycardia (HR<50/min) (1.4%); AV block-total 1°, 2°, 3° (1.2%); 2° and 3° (0.8%); flushing (0.6%); elevated liver enzymes (see **WARNINGS**).

The following reactions, reported in 1.0% or less of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain.

Cardiovascular: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope. **Digestive System:** diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia. **Hemic and Lymphatic:** ecchymosis or bruising. **Nervous System:** cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence. **Respiratory:** dyspnea. **Skin:** arthralgia and rash, exanthema, hair loss, hyperkeratosis, maculae, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme. **Special Senses:** blurred vision. **Urogenital:** gynecomastia, impotence, increased urination, spotty menstruation.

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Effects of Preload Reduction on Mitral Flow Velocity Pattern in Normal Subjects

Marco O. Triulzi, MD, Diego Castini, MD, Maurizio Ornaghi, MD, and Erminio Vitolo, MD

In the last few years, alterations in transmitral diastolic flow pattern have been used to assess changes in left ventricular diastolic properties. However, since diastolic flow primarily reflects the atrioventricular pressure gradient, loading conditions, as well as intrinsic left ventricular properties, should be able to affect this pattern. This study was selectively designed to decrease preload (a major determinant of the atrioventricular pressure gradient) in normal subjects to observe the effects on the Doppler transmitral flow pattern without pharmacologic interventions that may also affect left ventricular diastolic properties. In 12 normal subjects, preload was reduced by inflation of blood pressure cuffs placed at the level of the root of the 4 limbs. The peak velocity of early mitral flow (E wave) decreased from 62 ± 8 to 51 ± 7 cm/s ($p < 0.001$), while no changes were found in the maximal velocity after atrial contraction; this caused a significant decrease in the ratio of these 2 velocities (the E to A ratio) from 1.5 ± 0.3 to 1.1 ± 0.1 ($p < 0.001$). The time-velocity integral of early diastolic inflow decreased from 7.8 ± 1.3 to 6.1 ± 1.3 cm ($p < 0.001$) with no significant changes of the time-velocity integral of inflow after atrial contraction. Therefore, preload reduction in normal subjects significantly reduces transmitral flow in early diastole with preserved late ventricular filling, producing a pattern that can mimic the changes previously described in left ventricular diastolic dysfunction.

(Am J Cardiol 1990;66:995–1001)

From the Division of Cardiology, Bassini Hospital and University Department of Biomedical Sciences, Milan, Italy. Manuscript received December 20, 1989; revised manuscript received and accepted June 8, 1990.

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Doppler echocardiography is a relatively new noninvasive tool that can measure instantaneous blood flow velocities through the mitral valve orifice with relative ease and accuracy and can therefore determine the instantaneous pressure gradients developed between the left atrium and the left ventricle during ventricular filling by Bernoulli's equation.[1] Among the determinants of the atrioventricular pressure gradient, the diastolic properties of the left ventricle play an important role.[2–4] However, left ventricular filling reflects not only the diastolic properties of the left ventricle, but also hemodynamic factors, such as preload and afterload,[5,6] which contribute to the diastolic atrioventricular pressure gradient. The actions of these factors are complex and often ignored. Therefore, changes in the pattern of the left ventricular filling that have been attributed to altered diastolic ventricular properties[7–11] could also be produced or imitated by factors extrinsic to the ventricle. Among these factors, preload plays an important role in determining atrial pressure and hence left ventricular filling pressure.[5,12–14] Up to now, the effects of reduced left ventricular filling pressure on transmitral flow velocities in human beings have been studied only with pharmacologic agents, such as nitroglycerin.[15–18] This study was designed to evaluate the effects of preload reduction on transmitral flow velocity pattern in normal subjects using a nonpharmacologic maneuver to reduce venous return in order to avoid unwanted effects on other hemodynamic variables.

METHODS

Study population: Twelve subjects in whom cardiovascular diseases were ruled out by history, clinical examination, electrocardiography and cross-sectional and Doppler echocardiography were selected for the study. The subjects were all men; the mean age was 41 ± 13 years (range 23 to 65).

Study protocol: Doppler echocardiography studies were performed in basal conditions and 5 minutes after the simultaneous inflation of blood pressure cuffs at the root of the 4 limbs. The pressure of the cuffs was set at 10 mm Hg below the basal diastolic arterial pressure of each subject and kept constant until the echocardiographic examination was over.[19–21] The 5-minute inflation time was established according to previous studies and after a preliminary assessment in 5 subjects showed that this inflation time produced a stable plateau of decreased left ventricular end-diastolic dimensions, measured by a fixed M-mode ultrasound beam, without reflex tachycardia. Arterial blood pressure was measured

by cuff method before and after 5 minutes of cuffs inflation.

Echocardiography: The echocardiographic examinations were performed with a Hewlett-Packard 77020AC phased-array scanner, using a 2.5 MHz transducer for the pulsed-wave Doppler studies and a 3.5 MHz transducer for the cross-sectional and M-mode studies. All subjects were studied in a supine position rotated on the left side and the recordings taken during quiet respiration. Cross-sectional and M-mode images and Doppler signals were recorded with a simultaneous electrocardiographic lead on a half-inch videotape; M-mode tracings were also printed at a paper speed of 100 mm/s.

Doppler examinations: The size of the Doppler sample volume was set to optimize the Doppler signals and wall filters set at the lowest level. A standard apical 4-chamber view of the heart was obtained first and then the Doppler sample volume was placed in the inflow area of the left ventricle just below the level of the mitral anulus and its position adjusted until the maximal diastolic flow velocities were recorded. The depths used to obtain transmitral flow velocity profile were kept constant throughout each study. Subsequently, an apical 5-chamber view was obtained and the Doppler sample volume was placed just below the aortic leaflets. Minor adjustments of the sample volume position were made to obtain the maximal velocity profile in each subject. No corrections of the angle were made.

Cross-sectional examinations: To measure the mitral anulus diameter and to correlate changes in mitral flow pattern with changes in left atrial size and its variations during diastole, an apical 4-chamber view was recorded using American Society of Echocardiography criteria.[22]

M-mode examinations: To document changes in left ventricular size and obtain digitized measurements of diastolic parameters, M-mode recordings of the left ventricular cavity were recorded under the guide of the cross-sectional parasternal long-axis view, with the single beam positioned at the level of the tips of the mitral leaflets.

Quantitative assessment of Doppler signals: Doppler signals were traced using an analysis package built into the echocardiographic unit and after the modal velocity. The ascending and descending limbs of the E and A waves were linearly extrapolated to the baseline. The velocity signals that occurred during the period of diastasis were included, when present, in the contour of the total transmitral velocity profile. For each study before and after cuffs inflation, the velocity profiles of 5 beats were analyzed and averaged. The following parameters were measured: the peak velocity of the E and A waves; E- and A-wave duration; the total duration of ventricular filling; the time to peak of the E wave; the acceleration and deceleration of the E wave; and the time-velocity integrals of the E and A waves and of the total transmitral flow (Figure 1). Finally, the following values were derived: the ratio of the peak velocities of the E and A waves; the ratio of the time-velocity integrals of the E and A waves; the peak velocities of the E and A waves normalized to the total time-velocity integral of the transmitral flow (the former being equivalent to the peak volumetric filling rate normalized to stroke volume)[15,23] and the ratio between the last 2 parameters. The contours of the aortic velocity were also traced to measure the peak velocity, the time-velocity integral and the time to peak velocity and the ejection time.

Quantitative assessment of cross-sectional parameters: To evaluate possible variations of mitral anulus dimensions due to changes in preload, the mediolateral diameter of the mitral anulus was measured in the apical 4-chamber view from the second or third video frame after the initial maximal opening of the valvular leaflets. The measurement was taken from the inner edge of the lateral border of the anulus to the inner edge of the medial border just below the insertion of the valvular leaflets.[24] To analyze the dynamics of the left atrial emptying throughout diastole, the area of the left

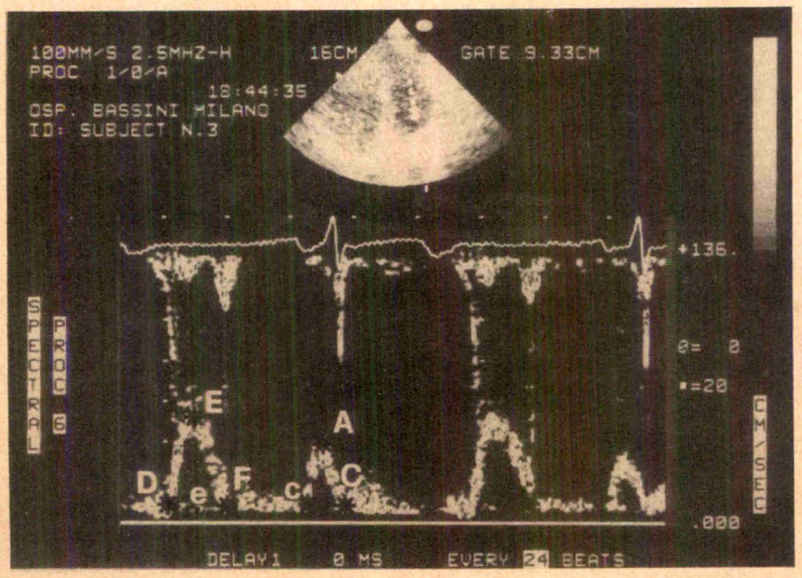


FIGURE 1. An example of measurements taken from a pulsed Doppler wave form of mitral flow velocity. A = peak velocity of late left ventricular filling; cC = A-wave duration; De = time to peak velocity of early filling; DE = acceleration of E wave; DF = E-wave duration; E = peak velocity of early left ventricular filling; EF = deceleration of E wave.

atrium in the apical 4-chamber view was measured as follows: at the frame before the mitral valve opening (LAA1), at the frame showing the smallest dimension in early diastole (LAA2), at the frame immediately before the reopening of the mitral leaflets due to the atrial contraction (LAA3), and at the frame showing the smallest atrial dimension after atrial contraction (LAA4). The percent changes of the left atrial area were calculated as follows: (LAA1 − LAA2)/LAA1; (LAA3 − LAA4)/LAA3; (LAA1 − LAA3)/LAA1; and (LAA1 − LAA4)/LAA1.

Quantitative assessment of M-mode parameters: To provide independent measures of the left ventricular diastolic filling, the M-mode echocardiographic tracings were analyzed using a computer device (Clinical Tracer Analyzer Numonics 1239) and a hand-controlled cursor. The resulting data represent the mean of the measurements obtained on ≥3 cardiac cycles. End-diastolic and end-systolic left ventricular internal diameters were measured according to American Society of Echocardiography standards[25] and left ventricular shortening fraction calculated according to the usual formula. The echocardiograms were then digitized by tracing endocardial echoes from the left side of the ventricular septum and from the posterior ventricular wall. From the digitized data, the computer derived the peak rate of internal diameter variation in diastole and systole, then normalized to the end-diastolic ventricular diameter (dD/dt/D).[26] Finally, on the left ventricular time-dimension curves, the measurements of the diastolic phases were obtained.[27]

Statistical analysis: All data are expressed as mean ± standard deviation. Student's paired 2-tailed *t* test was used to compare the measurements taken in the basal state and after cuffs inflation. A p value <0.05 was considered statistically significant.

RESULTS

Table I lists the comparison of clinical and echocardiographic parameters in the basal state and after cuffs

TABLE I Comparison of Clinical and Echocardiographic Parameters in Basal Conditions and After Cuffs Inflation

	Basal Conditions	After Cuffs Inflation	p Value
Age (yrs)	41 ± 13		
Heart rate (beats/min)	72 ± 16	72 ± 17	NS
Systolic blood pressure (mm Hg)	125 ± 10	124 ± 14	NS
Diastolic blood pressure (mm Hg)	80 ± 8	83 ± 9	NS
Doppler parameters			
Peak E-wave velocity (cm/s)	62 ± 8	51 ± 7	<0.001
Peak A-wave velocity (cm/s)	43 ± 10	46 ± 9	NS
E/A peak velocity	1.5 ± 0.3	1.1 ± 0.1	<0.001
E-wave velocity/time integral (cm)	7.8 ± 1.3	6.1 ± 1.3	<0.001
A-wave velocity/time integral (cm)	3.6 ± 1.0	3.8 ± 1.0	NS
E/A velocity/time integral	2.3 ± 0.6	1.7 ± 0.4	<0.002
Total velocity/time integral (cm)	13 ± 3	11 ± 3	<0.001
Normalized peak E-wave velocity	5.0 ± 1.0	4.9 ± 0.9	NS
Normalized peak A-wave velocity	3.4 ± 0.9	4.5 ± 1.2	<0.01
Normalized E/normalized A	1.5 ± 0.3	1.1 ± 0.1	<0.001
E wave time to peak (ms)	51 ± 12	51 ± 12	NS
Acceleration of E wave (cm/s^2)	1,344 ± 375	1,092 ± 336	<0.05
Deceleration of E wave (cm/s^2)	330 ± 92	228 ± 47	<0.001
E-wave duration (ms)	178 ± 25	182 ± 32	NS
A-wave duration (ms)	118 ± 25	122 ± 30	NS
Total integral duration (ms)	479 ± 179	471 ± 180	NS
Peak velocity of left ventricular outflow (cm/s)	95 ± 15	85 ± 13	<0.01
Left ventricular outflow velocity/time integral (cm)	18 ± 4	15 ± 4	<0.001
Left ventricular ejection time (ms)	290 ± 30	270 ± 30	<0.01
Left ventricular outflow time to peak (ms)	80 ± 10	80 ± 10	NS
Cross-sectional parameters			
Diameter mitral valve anulus (cm)	2.9 ± 0.4	2.9 ± 0.4	NS
Left atrium end-systolic area (cm^2)	17 ± 4	14 ± 3	<0.001
M-mode parameters			
Left ventricular diastolic diameter (mm)	53 ± 4	49 ± 4	<0.001
Left ventricular systolic diameter (mm)	33 ± 3	33 ± 3	NS
Left ventricular shortening fraction (%)	36 ± 5	31 ± 6	<0.001
Peak rate of diastolic ventricular dimension variation (s^{-1})	3.9 ± 0.8	3.0 ± 0.8	<0.001
Peak rate of systolic ventricular dimension variation (s^{-1})	2.6 ± 0.5	2.5 ± 0.6	NS
Isovolumic relaxation index (ms)	22 ± 16	22 ± 13	NS
% diameter increase during rapid filling	74 ± 9	63 ± 9	<0.05
% diameter increase during atrial contraction	13 ± 6	17 ± 9	NS

NS = not significant.

inflation. There were no significant changes in heart rate, systolic or diastolic arterial blood pressure after 5 minutes of cuffs inflation.

Doppler data: Blood pressure cuffs inflation produced a decrease of the peak velocity of the E wave with no changes of the peak velocity of the A wave; this caused a significant reduction of the ratio of the peak velocities of the E and A waves. The total time-velocity integral of the mitral flow decreased after cuffs inflation in the absence of changes in the duration of left ventricular filling. This was due to a decrease of the E wave time-velocity integral because A-wave time-velocity integral did not significantly change. As a result, the ratio of the time-velocity integrals of the E and A waves decreased. Finally, the peak velocity of the E wave normalized to the total time-velocity integral remained unchanged, whereas the peak velocity of the A wave normalized to the total time-velocity integral increased significantly; as a result, the ratio between these 2 parameters (E norm/A norm) decreased. A representative pair of Doppler signals of transmitral flow taken from a basal study and from the corresponding study after cuffs inflation are shown in Figure 2. The peak velocity of the aortic flow decreased after cuffs inflation as well as the time-velocity integral and the ejection time; the time to peak velocity did not change significantly.

Cross-sectional echocardiographic data: The diameter of the mitral anulus did not change after cuffs inflation. The left atrial area measured at the frame immediately before mitral opening (maximal area) was significantly decreased after cuffs inflation from the basal state and a significant difference between left atrial areas measured before and after cuffs inflation throughout the diastolic filling was also found (Figure 3); on the contrary, no significant differences were found between the percent changes of left atrial area during diastolic filling (Figure 4).

M-mode echocardiographic data: Left ventricular end-diastolic diameter decreased after cuffs inflation, while end-systolic diameter did not significantly change; this brought about a decrease in left ventricular shortening fraction. The peak rate of internal dimension varia-

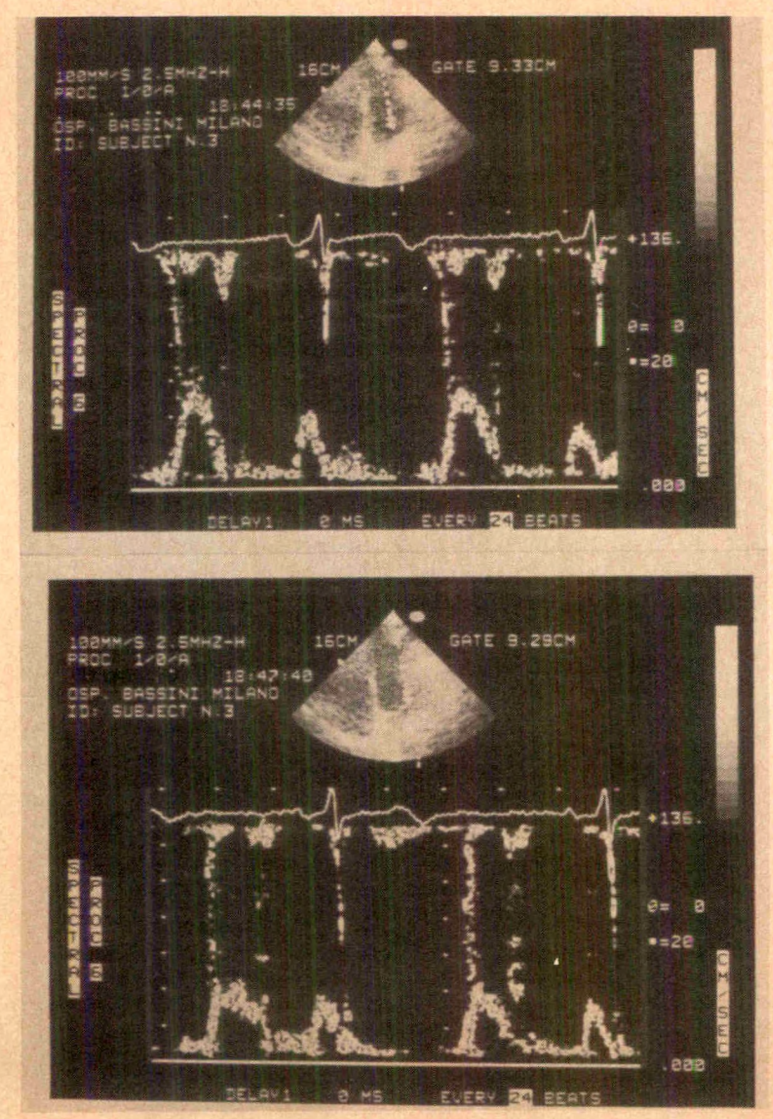


FIGURE 2. A representative pair of Doppler signals of transmitral flow taken from a basal study *(top)* and from the corresponding study after cuffs inflation *(bottom)*.

TABLE II Determinants of Left Atrial and Left Ventricular Pressures During Rapid Filling Phase and Atrial Contraction Phase

RFP	ACP
LAP	
Preload (pulmonary venous return)	Preload
Atrial compliance	Afterload (ventricular filling during early diastole)
LVP	
Afterload	Ventricular filling during early diastole
Preload	Chamber compliance
Contractility	Myocardial compliance
Active relaxation	
Elastic recoil	
Myocardial compliance	

ACP = atrial contraction phase; LAP = left atrial pressure; LVP = left ventricular pressure; RFP = rapid filling phase.

tion in early diastole and the percent ventricular diameter increase during rapid filling decreased. The isovolumic relaxation index did not show significant difference after cuffs inflation.

DISCUSSION

General considerations: Doppler echocardiography offers a unique possibility to study serially left ventricular filling that has often been taken to reflect left ventricular diastolic function. The Law of Conservation of Energy[1] affirms that the flow velocity across the mitral valve during left ventricular filling is strongly correlated to the instantaneous pressure gradients developed throughout diastole between the left atrium and the left ventricle; the intrinsic and hemodynamic factors affecting pressure in the left atrium and left ventricle are listed in Table II. The most accepted Doppler indexes of diastolic dysfunction may, therefore, be affected by changes in loading conditions. This may have a major clinical impact on the use of Doppler indexes for the evaluation of diastolic dysfunction.

Effects of preload reduction on transmitral flow pattern: Among the hemodynamic factors affecting left ventricular diastolic filling, preload appears to play an important role, as documented by recent experimental studies.[12–14] Few studies have shown the effects of preload reduction on Doppler transmitral velocity pattern in human beings. Choong et al[15] used a pharmacologic intervention (nitroglycerin infusion) to decrease preload in a group of patients with various cardiovascular diseases and receiving various drug treatments; after nitroglycerin infusion, they observed a decrease in the peak velocity and time-velocity integral of the E wave and in the total time-velocity integral of the transmitral flow. No changes were observed in peak velocity and time-velocity integral of the A wave. Therefore, the ratios between peak velocities and between time-velocity integrals of the E and A waves decreased. Similar results were obtained by other investigators using nitroglycerin for preload reduction.[16–18]

The main characteristics of our study were that we used a nonpharmacologic intervention to reduce preload and we studied subjects with normal basal diastolic function who were free from drug therapy. Our results show that inflation of blood pressure cuffs determines a reduction of venous return that induces a small but highly significant decrease of left atrial area (19%) and of left ventricular end-diastolic diameter (7%), without producing hypotension or reflex tachycardia.[28] This change in preload also decreases the peak velocity and the time-velocity integral of the E wave; the peak velocity and the time-velocity integral of the A wave do not change and hence a decrease in the ratios between E- and A-wave peak velocities and time-velocity integrals

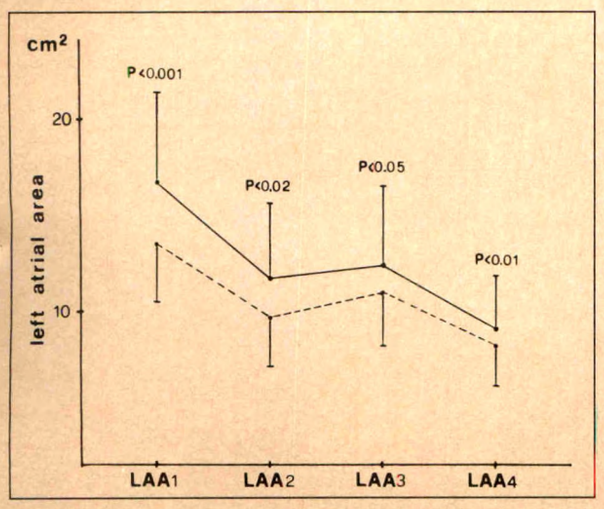


FIGURE 3. Left atrial areas (LAA1 = end-systolic area; LAA2 = smallest area in early diastole; LAA3 = area just before mitral reopening; LAA4 = smallest area after atrial contraction) in basal conditions *(points connected by the solid line)* and after cuffs inflation *(points connected by the broken line)* throughout diastole. *Bars* represent standard deviation values. Statistically significant levels are provided for the comparison between basal and postinflation atrial areas.

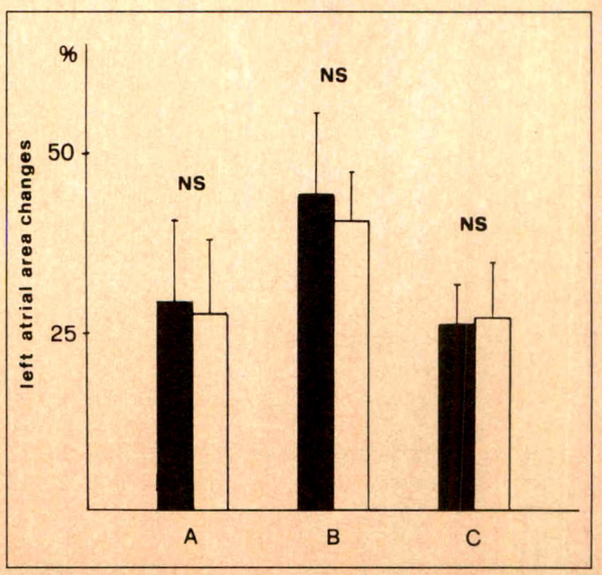


FIGURE 4. Comparison between left atrial area percent changes in basal conditions *(black bars)* and after cuffs inflation *(white bars)*. NS = not significant. A = (LAA1 − LAA2)/LAA1; B = (LAA1 − LAA4)/LAA1; C = (LAA3 − LAA4)/LAA4.

results. These data are consistent with the study by Choong et al.[15] Our study confirms that in the evaluation of ventricular diastolic function, the Doppler-derived indexes should be interpreted with considerations for variation in preload. In contrast to the study by Choong et al, we found that the peak velocity of the E wave normalized for the total time-velocity integral of the mitral flow does not change after preload reduction; moreover, we observed an increase of the peak velocity of the A wave normalized for the total time-velocity integral. These observations suggest, in our opinion, that the reduction of the peak velocity of the E wave is directly related to the reduction of the preload and that the normalized peak velocity of the E wave could potentially be an index independent from preload variations. The decrease of this index observed by Choong et al[15] might be explained by the complex effects of nitroglycerin on loading conditions and on ventricular relaxation.[29,30]

Transmitral flow velocity redistribution due to preload reduction and its possible mechanisms: Our results show that preload reduction produces a decrease of the total amount of diastolic blood flow to the left ventricle, as indicated by the decrease of the time-velocity integral of the transmitral flow in the absence of dimensional changes of the mitral anulus. Preload reduction was also found to redistribute the flow in diastole as indicated by the changes in the pattern of transmitral flow. The determinants of the left atrial and ventricular pressures during diastole are listed in Table II.

The following are our observations about the potential mechanisms for the redistribution of flow during left ventricular filling.

Rapid filling phase: As shown in Figure 3 and listed in Table I, left end-systolic atrial area and end-diastolic left ventricular dimensions decreased significantly after cuffs inflation. Assuming the absence of variations in atrial compliance in our normal subjects, this decrease suggests a decrease in preload. On the other hand, the left ventricular end-systolic diameter (an acceptable index of end-systolic volume) and the isovolumic relaxation index measured by M-mode echocardiography did not change after preload reduction; the peak rate of ventricular dimensions variation in early diastole obtained by digitized M-mode echocardiography decreased with the reduction of the "relaxation load" due to preload reduction.[6] We can assume that myocardial compliance and myocardial contractility were normal in our healthy subjects and that they most likely did not change throughout the study (the peak rate of left ventricular dimension change in systole and the time to peak of the aortic flow velocity were not modified by preload reduction). We can conclude, therefore, that the major determinant of the reduction of Doppler flow velocity during rapid filling is the reduction of atrial pressure due to the decrease in preload induced by cuffs inflation.

Atrial contraction phase: Our study (see Figure 3) shows that after cuffs inflation, the left atrial area decreases before mitral valve reopening. This suggests that there is reduced preload at the beginning of the late filling. On the other hand, the impedance to left atrial emptying is reduced too, according to the decrease of the left ventricular diameter percent variation during rapid filling measured by digitized M-mode echocardiography (that represents the fractional filling of the ventricle during early diastole). As shown in Figure 4, there are no differences in the percent of atrial area reduction in late diastole (atrial area at the frame immediately before mitral valve reopening versus the smallest area after atrial contraction) before and after blood pressure cuffs inflation. This suggests that the atrial dynamic is not altered during late filling phase. In our study, the reduction of preload makes the left ventricle work in a higher chamber compliance condition (lower point on the pressure/volume curve), determining most likely a reduction of the left ventricular pressure during atrial contraction. From these data, we can speculate that the peak velocity and the integral of the A wave do not change, because, in spite of a reduction of preload, the atrioventricular pressure gradient and the amount of ventricular filling in late diastole are kept constant by a parallel afterload reduction to atrial contraction. We can therefore conclude that any interpretation of the transmitral velocity pattern in terms of diastolic function should take into account the redistribution in transmitral flow induced by preload reduction.

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Clinical and Hemodynamic Assessment of the Hepatojugular Reflux

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The hepatojugular reflux (HJR) test was studied to assess the ability to clinically predict response during cardiac catheterization and to determine its significance in patients without heart failure and correlate it to their baseline hemodynamic parameters. Sixty-five patients considered to be free of heart failure undergoing routine cardiac catheterization were enrolled. The HJR test, defined as the venous pressure response to sustained abdominal compression, was performed in a standardized manner at the bedside assessing change in internal jugular venous pressure and during right-sided cardiac catheterization measuring change in right atrial pressure. For comparison a sustained increase ≥1 cm was considered positive. In 62 of 65 patients the HJR test stabilized by 15 seconds. The results during examination at the bedside agreed with those at catheterization (κ = 0.74, p <0.001). The HJR test result correlated best with baseline mean right atrial pressure (r = 0.59) and right ventricular end-diastolic pressure (r = 0.51), and in bivariate regression analysis predicted right atrial ($F_{(1,63)}$ = 32.8, R^2 = 0.34, p <0.0001) and right ventricular end-diastolic ($F_{(1,63)}$ = 22, R^2 = 0.26, p <0.0001) pressures. A positive test had high sensitivity and specificity for predicting right atrial pressure >9 mm Hg (1.0, 0.85) and right ventricular end-diastolic pressure >12 mm Hg (0.90, 0.89). It is concluded that 15 seconds is adequate for interpretation, and bedside observation predicts the response during right-sided cardiac catheterization. A positive test result in patients believed clinically free of heart failure can detect elevated right-sided cardiac pressures and correlated best to baseline mean right atrial and right ventricular end-diastolic pressures. This suggests a central role of right-sided cardiac function in determining the response.

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The hepatojugular reflux (HJR) test was first described by Pasteur in 1885[1] as a physical sign of tricuspid regurgitation. It has subsequently been believed to be useful in the diagnosis of congestive heart failure.[2] The HJR test involves observation of the jugular veins while applying sustained pressure to the abdomen. The site of abdominal compression does not influence the interpretation of the maneuver.[2,3] Evidence now suggests that venous pressure must remain elevated only 10 seconds[4] for the test to be considered positive. The increase above baseline of the jugular venous pressure during the HJR test that is considered normal has been stated to be from 1[5] to 3[4] cm.

A positive test has previously been thought to indicate decompensated right ventricular function.[3,6] Hitzig[6] believed it was one of the earliest signs of cardiac failure. Hemodynamic correlation of this test is available in only 2 studies.[4,7] It was suggested that a positive test correlated best with a pulmonary capillary wedge pressure of >15 mm Hg.[7] This study was designed to determine if the test performed at the bedside predicts the response recorded during right-sided cardiac catheterization, and to assess the significance of the HJR test in a patient population without overt clinical heart failure and correlate it to their baseline hemodynamic parameters.

METHODS

Patients: Sixty-five patients undergoing routine diagnostic cardiac catheterization for ischemic or valvular heart disease were studied between November 1987 and March 1988. Subjects were examined without knowledge of their history or indication for catheterization, and the results of 1 or the agreement of 2 observers were recorded. Subjects had coronary artery disease alone (n = 40), valvular heart disease alone (n = 6), neither (n = 15), or both (n = 4). Only patients without evidence of overt heart failure, as assessed by clear lung fields, absent S_3 and normal jugular venous pressure were included. The jugular venous pressure was defined as the end-expiratory peak pulsation of the internal jugular vein and a level of ≤4 cm above the sternal angle at 30 degrees was considered normal.

Hepatojugular reflux test: The HJR test was initially performed at the bedside. To compare the results of this examination with that obtained during right-sided cardiac catheterization, a sustained elevation of >1 cm was considered positive. The test was standardized, in a manner similar to that of Ducas et al,[4] by applying continuous pressure to a semiinflated blood pressure cuff

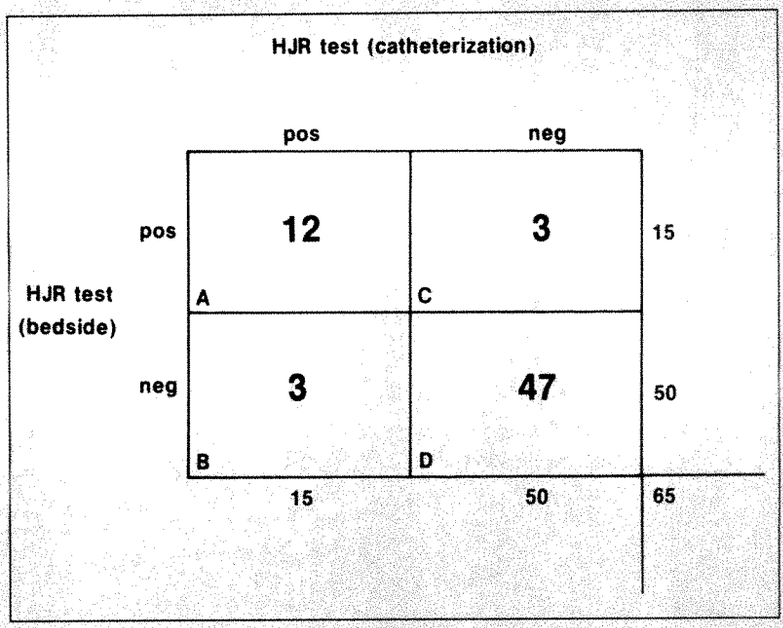


FIGURE 1. Prediction of hepatojugular reflux (HJR) test result (change in right atrial pressure) at catheterization from HJR test result (change in jugular venous pressure) observed at the bedside. Sensitivity = A/A+B, = 0.80; specificity = D/C+D, = 0.94; κ = 0.74, p <0.001. neg = negative; pos = positive.

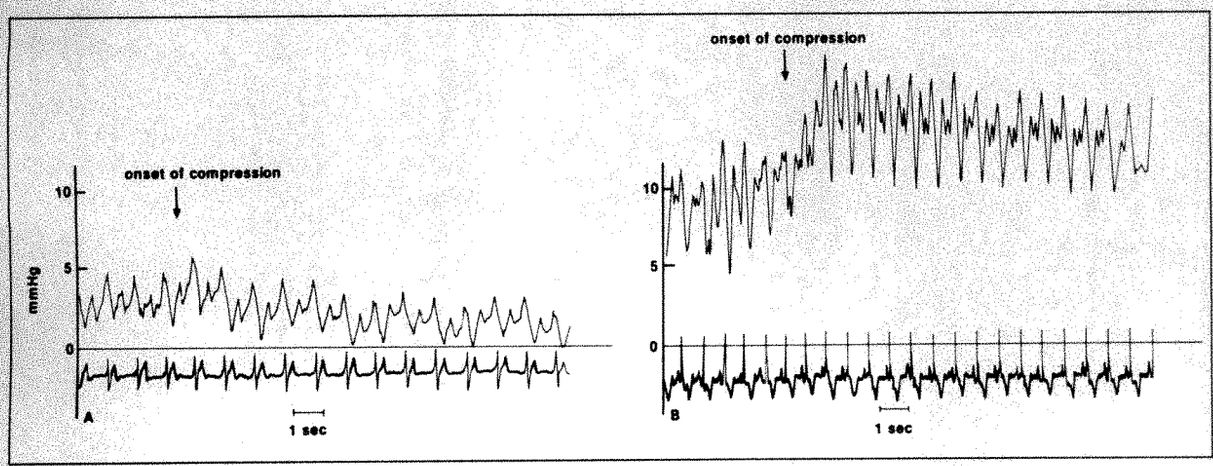


FIGURE 2. Example A indicates a negative hepatojugular reflux test. Example B represents a positive test.

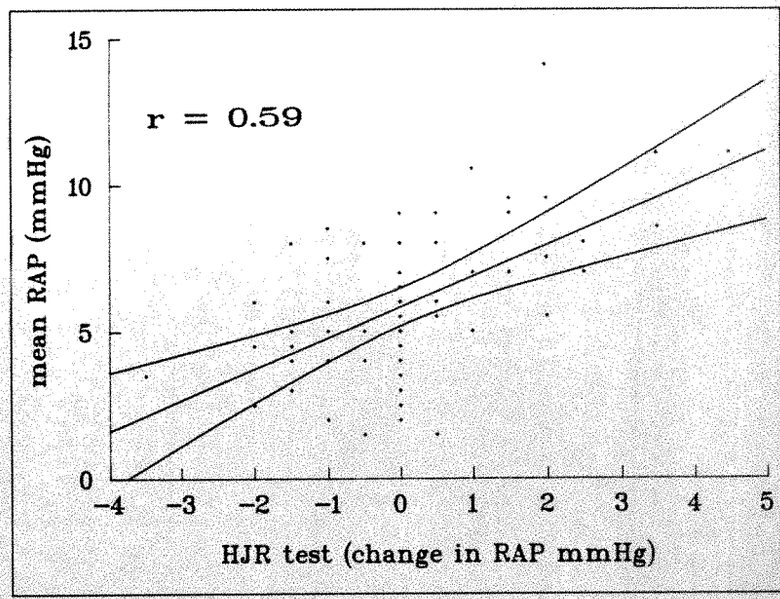


FIGURE 3. Scatter plot of baseline mean right atrial pressure (RAP) versus hepatojugular reflux (HJR) test result (absolute change in RAP with abdominal compression) with regression line and 95% confidence interval.

TABLE I Correlation of Hepatojugular Reflux (HJR) Result (Absolute Change in Right Atrial Pressure to Abdominal Compression in mm Hg) with Baseline Hemodynamic Parameters

	HJR Test Result			
Parameter	r	F	R^2	p
Right atrial pressure (mm Hg)	0.59	32.8	0.34	<0.0001
Right ventricular end-diastolic pressure (mm Hg)	0.51	22.0	0.26	<0.0001
Pulmonary capillary wedge pressure (mm Hg)	0.38	10.5	0.15	0.002
Pulmonary artery pressure (mm Hg)	0.18	2.2	0.03	0.14
Left ventricular end-diastolic pressure (mm Hg)	0.15	1.3	0.02	0.26
Ejection fraction (%)	0.03	0.05	0.001	0.83

TABLE II Sensitivity, Specificity and Predictive Values of a Positive Hepatojugular Reflux Test (Increase >1 mm Hg in Right Atrial Pressure) to Detect Resting Levels of Right Atrial and Right Ventricular End-Diastolic Pressures

			Predictive Value	
Parameter (mm Hg)	Sensitivity	Specificity	+	–
Right atrial pressure >8	0.73	0.87	0.53	0.94
Right atrial pressure >9	1.0	0.85	0.40	1.0
Right ventricular end-diastolic pressure >8	0.41	0.92	0.80	0.66
Right ventricular end-diastolic pressure >12	0.90	0.89	0.60	0.98

+ = positive; – = negative.

taped to the epigastrium sufficient to raise a mercury column 35 mm. Subjects were instructed to maintain quiet breathing through an open mouth during this procedure. The location and degree of pressure exerted is similar to that used in routine clinical practice.

Cardiac catheterization: Right-sided cardiac catheterization was performed through the femoral vein approach using a Cournand catheter and a fluid-filled system leveled to midchest. Pulmonary capillary wedge, mean pulmonary artery, right ventricular end-diastolic and right atrial pressures were recorded. To compare the results at bedside examination with those at catheterization, centimeters of water were converted to millimeters of mercury. With the catheter in the midright atrial position a repeat HJR test was performed. The change in right atrial pressure, compressing for a minimum of 45 seconds, was recorded. Left-sided cardiac catheterization followed with measurement of left ventricular end-diastolic pressure and performance of left ventricular angiography in the right anterior oblique projection for calculation of ejection fraction.

Statistical analysis: The HJR test result determined at the bedside was compared with that obtained during right-sided cardiac catheterization using a κ statistic. Baseline hemodynamic parameters were correlated to the absolute change in right atrial pressure during the HJR test using the Pearson correlation coefficient (r). Bivariate regression analysis was performed using the HJR test result as the independent variable and the baseline hemodynamic parameters as the dependent variables generating F (variance ratio) and R^2 values. Stepwise multiple regression analysis was performed using the baseline hemodynamic parameters in a model to predict a positive HJR test.

RESULTS

In 62 of 65 subjects the right atrial pressure response to abdominal compression stabilized by 15 seconds. In most of the subjects it stabilized earlier and remained constant for 45 to 60 seconds of observation. In 3 sub-

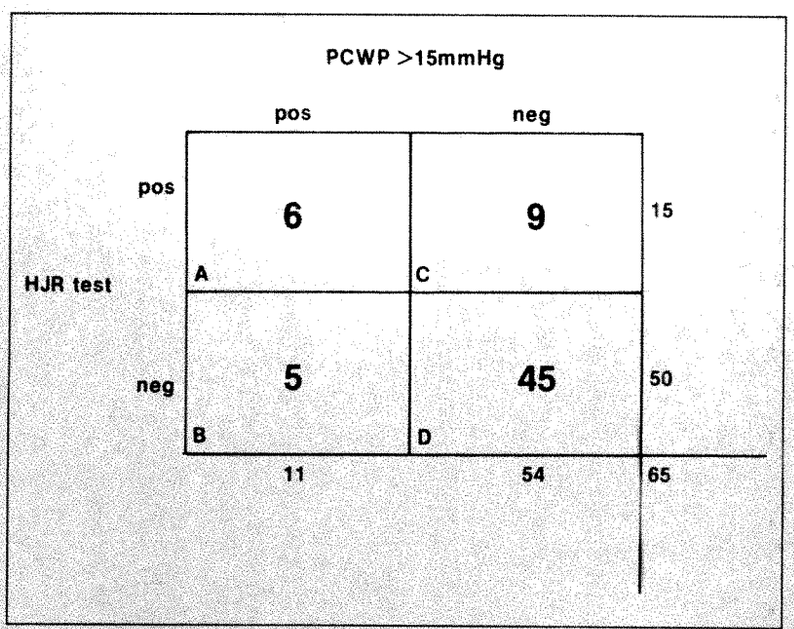


FIGURE 4. Ability of a positive (pos) hepatojugular reflux (HJR) test (>1 mm Hg increase) to predict pulmonary capillary wedge pressure (PCWP) >15 mm Hg. Sensitivity = A/A+B, = 0.55; specificity = D/C+D, = 0.83; positive (pos) predictive value = A/A+C = 0.40; negative (neg) predictive value = D/B+D = 0.90.

jects there was a delayed return to baseline of borderline positive tests after 33 to 50 seconds. These 3 tests were classified as negative for analysis, although results were not influenced if they were considered positive.

Fifteen patients had a positive HJR test at catheterization. Tests in 12 of the 15 had been assessed as clinically positive and 3 as negative. Of the 50 patients with negative tests during catheterization, 47 had clinically negative and 3 had positive results. These results are demonstrated in Figure 1 and show a κ value of 0.74 ($p < 0.001$) for the comparison of bedside examination with the results at catheterization. Observation of the right atrial pressure revealed that the end-expiratory peak transiently increased with the onset of abdominal compression in most subjects. It remained elevated (≥ 1 mm Hg) in 15 subjects (the positive HJR group), returned to baseline in 32 and decreased (≥ 1 mm Hg) in 18. Examples of a negative and positive test are shown in Figure 2.

The absolute change in right atrial pressure during the HJR test, whether an increase or decrease, was correlated with baseline hemodynamic parameters providing the correlation coefficients (r values) listed in Table I. The correlation is strongest with baseline mean right atrial ($r = 0.59$) and right ventricular end-diastolic ($r = 0.51$) pressures and is positive, indicating that the higher the baseline values of these parameters the more positive is the HJR test result. Figure 3 is a scatter plot of the HJR result versus baseline mean right atrial pressure. Bivariate regression analysis was performed using the absolute change in right atrial pressure during the HJR test as the independent variable and the baseline parameters as the dependent variables since it would be most useful if the HJR result was predictive of hemodynamic parameters in a population without clinical heart failure. The F and corresponding R^2 values from this analysis are listed in Table I. These indicate a high degree of significance for prediction of baseline mean right atrial and right ventricular end-diastolic pressures from the HJR result ($p < 0.0001$). A less significant result is seen for pulmonary capillary wedge pressure. Stepwise multiple regression analysis was performed with the baseline hemodynamic parameters used in a model to predict a positive HJR test. The only hemodynamic variable that remained in the model was the baseline mean right atrial pressure ($p < 0.0001$).

The sensitivity, specificity and predictive value of a positive HJR test (≥ 1 mm Hg increase) for determining different degrees of abnormality in baseline hemodynamic measurements were calculated. Figure 4 demonstrates a 2 by 2 table where the HJR test is used to predict a wedge pressure >15 mm Hg. The sensitivity is only 0.55, the specificity 0.83 and the positive predictive value 0.40. In a similar manner other tables were constructed and the results of 4 of these are shown in Table II. Mean right atrial and right ventricular end-diastolic pressures >8 mm Hg were chosen as they represent quoted upper limits of normal.[8] Mean right atrial pressure >9 mm Hg and right ventricular end-diastolic pressure >12 mm Hg were chosen as they demonstrate the highest degree of sensitivity and specificity. All 6 patients with mean right atrial pressure >9 mm Hg and 9 of 10 patients with right ventricular end-diastolic pressure >12 mm Hg had positive tests. A positive HJR test identifies most patients who are clinically considered to have normal jugular venous pressure but have abnormal right-sided cardiac pressures at catheterization. The high negative predictive values in Table II indicate that a negative HJR test supports the clinical impression of normal right-sided pressures in these patients.

DISCUSSION

The stated duration of abdominal compression required to interpret the HJR test accurately has varied. The results of this study support the conclusions of Ducas et al[4] who believed only 10 seconds was necessary for stabilization of the response. An observation period of 15 seconds is sufficient to classify patients correctly into a positive or negative response. In this patient group the interpretation of the HJR test during bedside examination predicted the response at right-sided cardiac catheterization in most cases.

We chose a patient population without overt clinical evidence of heart failure because a positive test in these patients would be most useful if it was found to correlate with or predict abnormalities of resting pressures. Internal jugular venous pressure estimated at the bedside may not accurately represent directly measured right atrial pressure in all cases.[9] By performing the HJR test, the change in venous pressure can be observed regardless of absolute level. In this patient group, considered clinically to have normal venous pressures, a positive HJR test was associated with elevated right-sided cardiac pressures at catheterization. A negative test confirmed the clinical belief that the resting pressures were in the normal range. False positives and negatives did occur.

One would predict that if the change in right atrial pressure with abdominal compression correlated with resting pressures it would do so in a continuous manner. A more positive HJR test should occur with more abnormal resting pressures. We found that the absolute change in right atrial pressure that occurred with the test correlated positively with the level of baseline mean right atrial and right ventricular end-diastolic pressures. This was also seen in bivariate regression analysis. In stepwise multiple regression analysis only the baseline mean right atrial pressure was retained in the model to predict the HJR test result. These results would support the conclusion that a positive HJR test best correlates with the functional status of the right heart. Either abnormal right-sided volume or compliance, with an abnormal pressure-volume curve, could account for these findings.

Other investigators have postulated mechanisms of a positive response. Ewy[7] suggested that an elevated wedge pressure was the most important factor, although a positive response could be seen in right ventricular infarction without wedge pressure elevation; he believed

that this supported increased pulmonary vascular volume as an important mechanism. Our study was completed before publication of information that a positive test suggests pulmonary capillary wedge pressure ≥15 mm Hg but does not confirm the usefulness of that observation.

The correlation coefficients obtained in this study, although highly statistically significant, are modest in degree, suggesting that the mechanism of a positive response is multifactorial. Dysfunction of the right heart, either primary or secondary to abnormalities of the left heart, pericardium or other intrathoracic structures may play a central role.

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Anatomic Correlations of the Long-Axis Views in Biplane Transesophageal Echocardiography

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The number of views obtainable during transesophageal echocardiography (TE) has been limited by the fixed position of the transducer at the end of the probe. This has confined standard TE studies to short-axis tomography of the heart and aorta. Recently, a biplane TE probe has become available that is capable of both long- and short-axis imaging. This study prospectively assessed the application of the long-axis plane of the biplane probe in providing complementary long-axis views in ambulatory patients. Six standard long-axis views could be obtained and were compared with corresponding anatomic sections to illustrate anatomic relations and facilitate structure identification. The long-axis views provide a better appreciation of the 3-dimensional nature of cardiac anatomy and function, especially in demonstrating the relation of vertically aligned structures.

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Proximity to the heart and freedom from acoustic interference generally permit excellent image quality during transesophageal echocardiography (TE).[1–5] There has been remarkable progress of TE technology since its inception. The milestones include the advent of real-time scanning with a mechanical transducer, real-time phased-array imaging on a deflectable endoscope, and the addition of color Doppler capability.[6–13]

Different structures can be imaged, depending on the depth of probe insertion and the orientation of the transducer. Transducer rotation, to obtain short- and long-axis views from a single acoustic window, is a simple manipulation during precordial examination but has not been technically feasible during TE imaging. So far, TE studies have only been performed using a short-axis imaging transducer; thus, the imaging planes of TE have been restricted to variations of short-axis tomography.[1–5] A new biplane TE probe has been developed which is capable of imaging in the long-axis plane in addition to the familiar short-axis plane. To appraise this new tool, this study sought to define the standard views of the heart and great vessels obtainable with long-axis imaging, and to assess the utility of long-axis sections of specific cardiac structures by comparison with corresponding anatomic sections.

METHODS

Equipment: The biplane probe (ALOKA) consists of two 5-MHz phased-array ultrasound transducers with perpendicular crystal alignment at the end of an endoscope (Figure 1). The proximal transducer generates long-axis images. Short-axis images originate from the distal transducer. The endoscope is 1 m long and 9 mm thick. The tip of the endoscope is 29.5 mm long, 13.5 mm wide and 9 mm thick. The probe connects to an ALOKA 870 color Doppler echocardiographic machine. A control button on the machine determines which of the 2 transducers is active. Both short- and long-axis images can be captured in a cine-loop format and displayed simultaneously on a split screen. Two control knobs permit anteroposterior and right-left deflection of the tip of the probe for further modification of the imaging plane.

Patients: Biplane TE studies were performed in 37 consecutive awake patients (15 women and 22 men [mean age ± standard deviation 52 ± 15 years, range 18 to 74]) with a spectrum of cardiovascular diseases. The reasons for patient referral included suspected aortic disease in 9 patients, aortic valve abnormalities in 5,

mitral valve abnormalities in 9, atrial abnormalities in 7, complex congenital heart disease in 4, cardiomyopathy in 2 and cardiac tumor in 1.

Procedure: The patient preparation and technique of TE in awake patients have been previously described.[2,4] Informed consent was obtained. Standard short-axis views were obtained by changing the depth and deflection of the probe. For each standard short-axis view identified, the long-axis transducer was activated and the corresponding long-axis image of the same structures was attempted. Probe insertion and angulation were modified slightly when changing imaging planes to maintain an acoustic window on the same anatomy from the same vantage point within the esophagus.

Long-axis images obtainable in all patients were deemed the standard views of long-axis TE imaging. The use of the 2 planes in revealing anatomic structures and relations were assessed. Fixed specimens of the human heart were sliced to illustrate the anatomy underlying the long-axis images better.

RESULTS

Standard views: Six long-axis TE tomographic views were obtainable and found to be particularly useful. With the imaging transducer positioned at the level of the aortic valve, right to left rotation of the probe produced 4 sequential long-axis tomographic views of cardiac structure. The views were right atrium and venae cavae, left ventricular outflow tract, right ventricular outflow tract, and left atrium and mitral valve (Figure 2, a to d). The long-axis view of the left ventricle was obtained from a transgastric vantage point (Figure 2e), and those of the descending aorta with the transducer facing posteriorly and leftward (Figure 2f).

Anatomic correlations: The long-axis plane was useful to show the continuity of the venae cavae with the right atrium (Figure 2a and 3). The superior vena cava and its relation to the atrial septum were well visualized. The right pulmonary artery could be seen in its short axis directly behind the superior vena cava. A long segment of the ascending aorta could be visualized with the imaging plane rotated slightly to the left (Figure 2b and 4). The blind spot of the ascending aorta, usually present during short-axis imaging as a result of the interposing trachea, was reduced. The left ventricular outflow tract was also better seen as it was now more aligned with the ultrasound beam. With further leftward rotation of the long-axis imaging plane, the right ventricular outflow tract could be well visualized (Figure 2c and 5). There was also a good view of the main pulmonary and the proximal right and left pulmonary arteries. The last long-axis view at this level revealed the anteroposterior relation of the mitral leaflets (Figure 2d and 6). Slight leftward or rightward rotation from this view would allow assessment of different scallops of the mitral leaflets, thus permitting a more comprehensive assessment of mitral anatomy. The left atrial appendage could also be well seen at this point, particularly with regard to its continuity with the left atrium and its proximity to the mitral valve.

The long-axis views of the left ventricle and descending thoracic aorta could be obtained from the acoustic windows corresponding to the short-axis tomographic views. The long-axis view of the left ventricle (Figure 2e and 7) gave a different perspective for the evaluation of left ventricular wall motion. The anterior and inferior walls of the left ventricle were usually visualized, although different regions of the left ventricle could be imaged by rotating the long-axis plane. However, with-

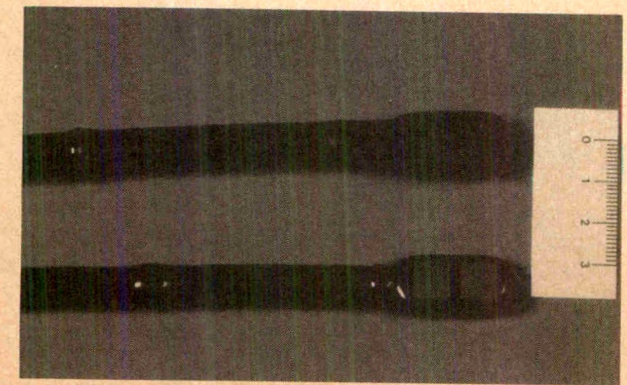


FIGURE 1. Photograph of biplane transesophageal probe with short-axis probe. The imaging surfaces of biplane probe are square-shaped and adjacent to each other at the end of the probe. Biplane probe is only slightly larger than short-axis probe.

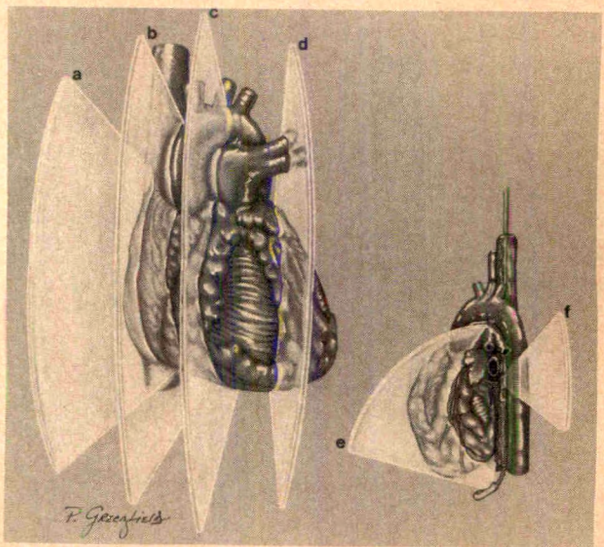


FIGURE 2. Drawing of 6 standard, long-axis tomographic sections through the heart and aorta. Sections *a* to *d* are derived from a transducer position behind the base of the heart. With right to left rotation of the probe, the following sections of the heart are obtained: *a*, right atrium, venae cavae, atrial septum; *b*, left ventricular outflow tract, aortic valve, ascending aorta; *c*, right ventricular outflow tract, pulmonic valve, pulmonary artery; *d*, left atrium and appendage, mitral valve, left ventricle. Section *e* generates a transgastric tomogram of the mid- and apical left ventricle. With posterior rotation of the transducer, longitudinal section of the descending aorta is obtained (*f*). At a higher level, long-axis imaging would produce a cross section of the aortic arch (not shown).

out a proper internal reference point, it was often difficult to ensure transection of the true left ventricular apex. The long-axis view of the descending aorta resembled the view obtained by aortography (Figure 2f and 8). The horizontally positioned aortic arch was seen in cross section when cut by a long-axis ultrasound plane, in contrast to the longitudinal cut of short-axis imaging.

DISCUSSION

There are important advantages of biplane TE imaging (Table I). It permits a better appreciation of 3-dimensional cardiac anatomy and function. Continuity between vertically aligned structures can be better demonstrated, and it may help distinguish artifact from real abnormality.

Atrial septum: This is particularly important in patients with enlarged aortic roots that distort the atrial septal configuration so that only a small portion of this structure can be seen on the short-axis view. Furthermore, the atrial septum and the venae cavae cannot be displayed in the same view using short-axis imaging. This important anatomic relation can be better visualized using the long-axis plane.

Right ventricular outflow tract: The right ventricular outflow tract is usually not well visualized by short-axis imaging. The long-axis plane gives a good view of

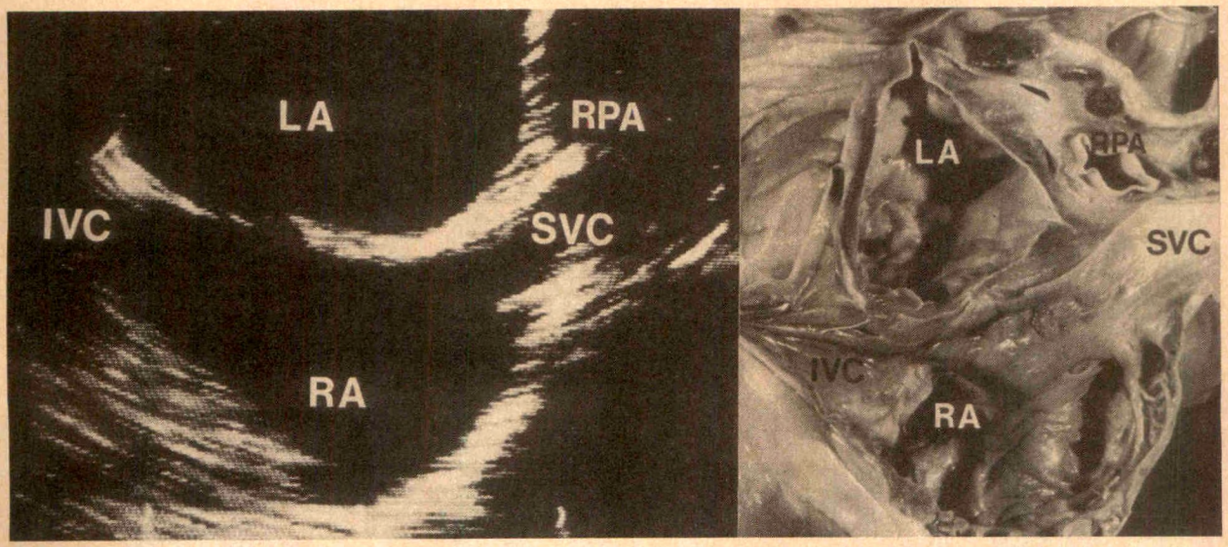


FIGURE 3. ***Left,*** **transesophageal echocardiographic long-axis scan showing continuity of the venae cavae, atrial septum and right atrium (RA). Septal thinning at the fossa ovale is apparent. The venae cavae can be followed longitudinally. The right pulmonary artery (RPA) is visualized in its short axis just posterior to the superior vena cava (SVC).** ***Right,*** **anatomic section corresponding to** ***left.*** **IVC = inferior vena cava; LA = left atrium.**

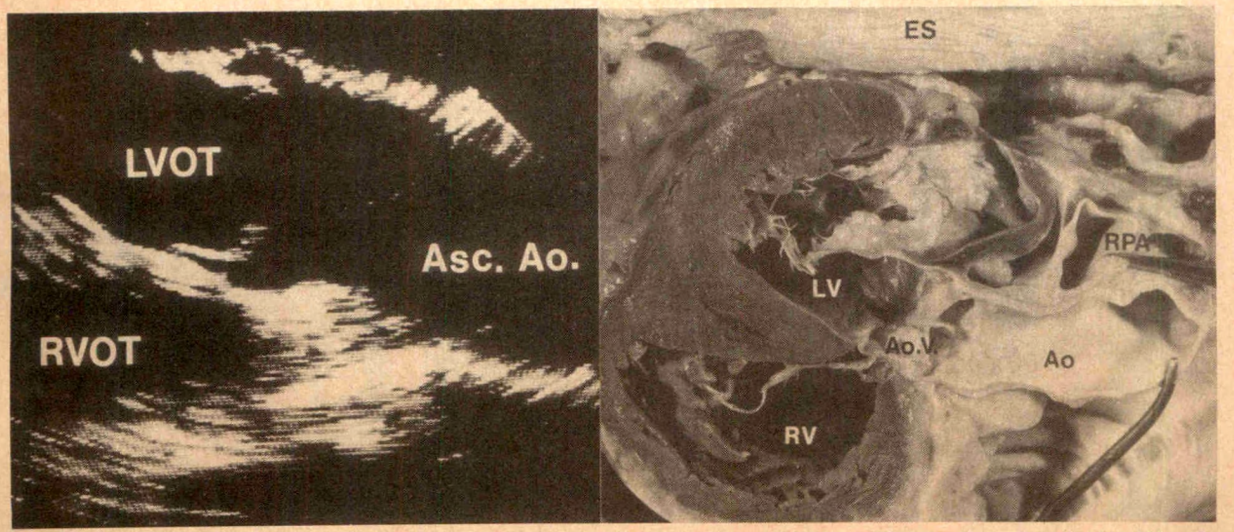


FIGURE 4. ***Left,*** **transesophageal echocardiographic long-axis view of the left ventricular outflow tract, aortic valve (Ao.V.) and ascending aorta (Asc. Ao.). The aortic valve demonstrated doming because it was bicuspid.** ***Right,*** **anatomic specimen cut to illustrate the tomogram at** ***left.*** **Ao = aorta; ES = esophagus; LV = left ventricle; LVOT = left ventricular outflow tract; RV = right ventricle; RVOT = right ventricular outflow tract; other abbreviations as in Figure 3.**

this region and can be invaluable in patients with obstructed right ventricular outflow tract or conduit. The relation of the right ventricular inflow to outflow tract is also demonstrated in this view.

Aortic valve: The aortic valve plane can be distorted in patients with dilated aortic roots or stenotic aortic valves. A true cross section or a true long-axis view of the aortic valve may not be obtainable by short-axis imaging but may become feasible by using the long-axis plane. Thus, potential errors in interpretation can be avoided.

Mitral valve: Biplane imaging provides a better visualization of the multiple scallops of the mitral leaflets, allowing a more thorough examination of the mitral valve in an expeditious fashion. Multiple regurgitant jets can be readily detected and the accuracy of the quantitation of mitral regurgitation may be enhanced.

Left ventricle: The short-axis plane may not be able to image the left ventricle distal to the level of the papillary muscles. In these patients more of the apical region may be seen using the long-axis plane. Although the long-axis view of the left ventricle may not provide an image of the true apex, it does allow assessment of regional wall motion from a different perspective. This may be used to follow serial changes.

Descending aorta: When the aorta is ectatic or tortuous, long-axis imaging permits a better visualization of the abnormality. This appears particularly important among patients with aortic dissection as intimal tears can be better imaged. The blind spot of the ascending

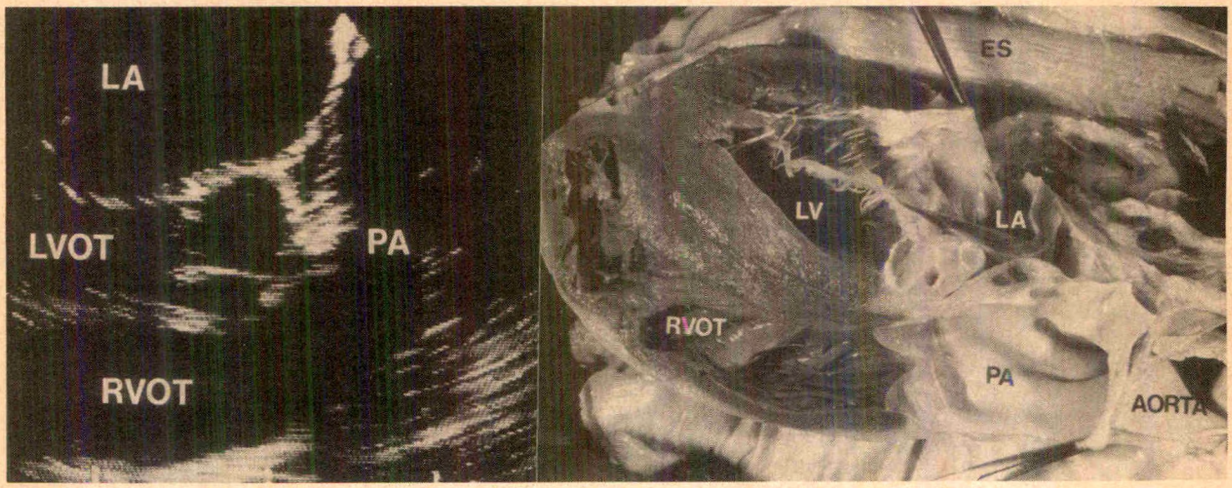


FIGURE 5. ***Left,*** **transesophageal echocardiographic long-axis scan of the right ventricular outflow tract (RVOT) and pulmonary artery (PA). The rather fine pulmonary valve is not clearly seen in this frame.** ***Right,*** **corresponding section of heart specimen illustrates the proximity of the 2 semilunar valves. Other abbreviations as in Figures 3 and 4.**

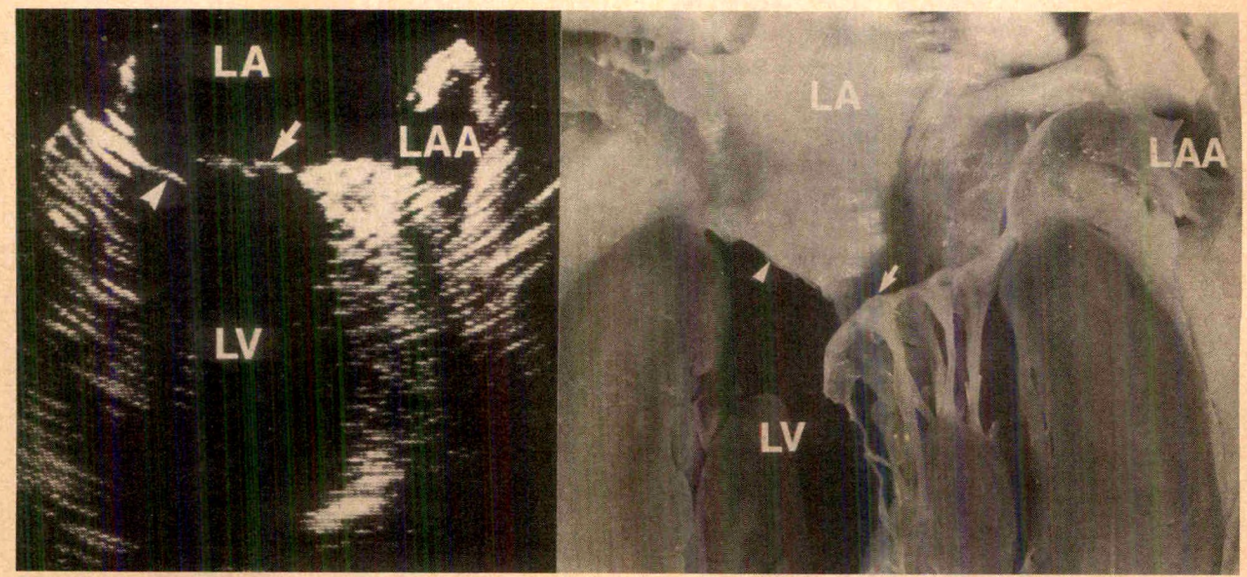


FIGURE 6. ***Left,*** **transesophageal echocardiographic long-axis scan of the left atrium (LA), left atrial appendage (LAA), mitral valve and left ventricle (LV). The anterior mitral leaflet (*arrow*) is shown adjacent to the left atrial appendage. Only a small segment of the posterior leaflet (*arrowhead*) is seen. Leaflet visualization varies considerably with transducer rotation.** ***Right,*** **anatomic section corresponding to *left*.**

TABLE I Cardiac Structures Visualized by Biplane Transesophageal Echocardiography

Structures	Advantage of Long-Axis Plane
Atrial septum	Better seen in patients with enlarged aortic root; relation to vena cavae demonstrated
Right ventricular outflow tract	Visualization of right ventricular outflow tract, including conduits
Aortic valve	Proper short-axis view and determination of the number of aortic cusps
Mitral valve	Better delineation of mitral leaflets and regurgitant jets
Left ventricle	May provide better assessment of regional function
Descending aorta	Clear visualization of pathology, particularly when the aorta is ectatic

aorta is reduced but not eliminated in biplane TE imaging.

Limitations: To incorporate the 2 sets of imaging elements on the tip of the transducer for biplane imaging, several technologic compromises are made. First, the size of the probe is slightly bigger. This does not appear to be a problem for esophageal intubation in adult patients. However, it does impose limitation to further miniaturization of the probe for pediatric use. Second, the number of elements in each imaging surface is reduced compared with that of the dedicated short-axis transducer. There is reduced image quality as a result. Last, the 2 imaging surfaces are mounted one above the other at the tip of the biplane endoscope. If the insertion of the probe is not adjusted when changing imaging

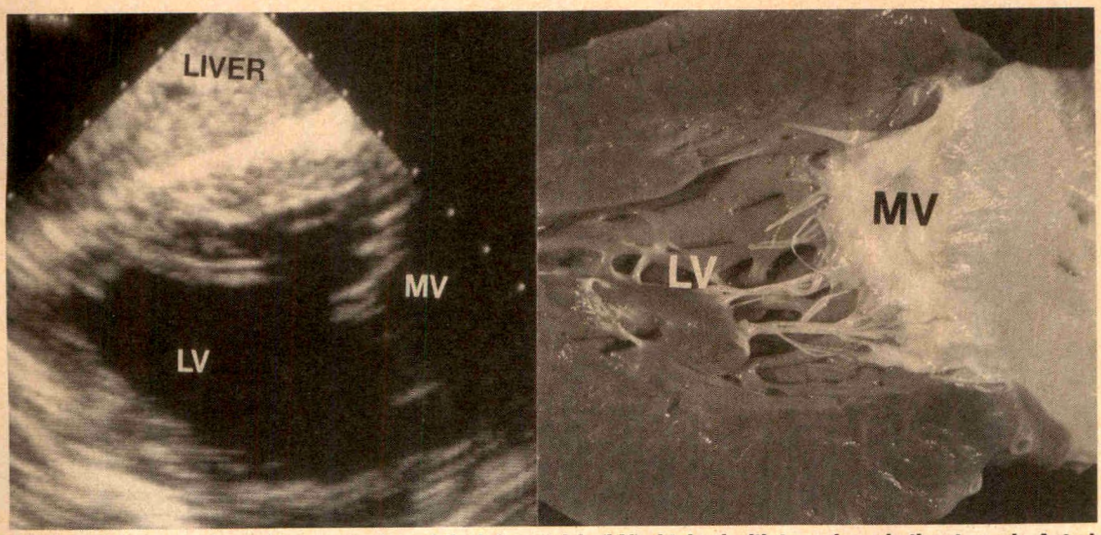


FIGURE 7. ***Left,*** **transesophageal long-axis view of the left ventricle (LV) obtained with transducer in the stomach. Anterior and inferior walls were imaged. Different regions of the left ventricle can be visualized depending on the sectioning plane. This view may not transect the true apex of the left ventricle (see text).** ***Right,*** **corresponding anatomic section of the left ventricle. MV = mitral valve.**

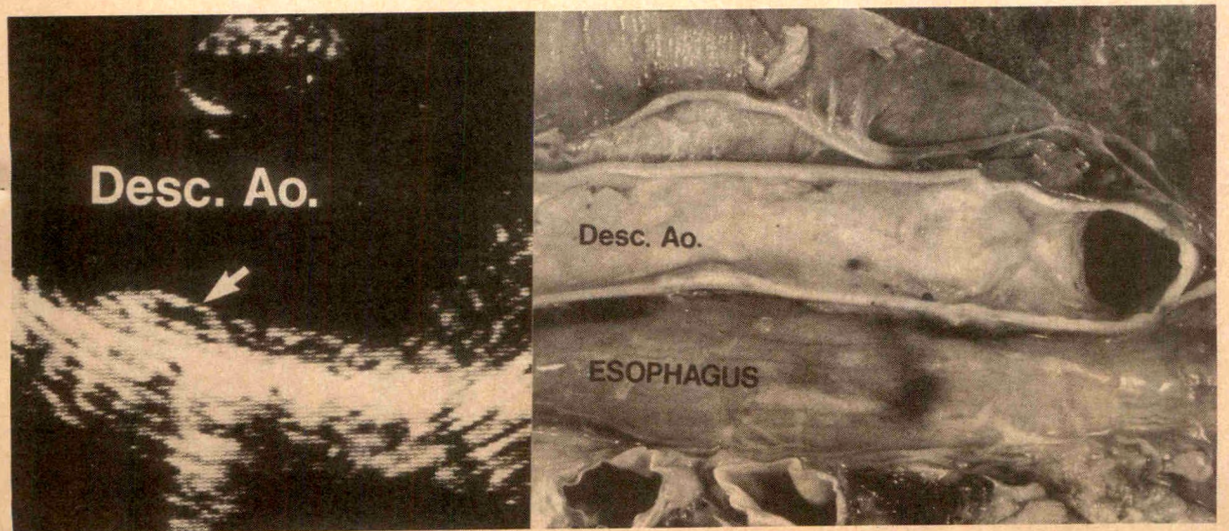


FIGURE 8. ***Left,*** **transesophageal echocardiographic long-axis scan of the descending aorta (Desc. Ao.). Atheromatous changes (*arrow*) are noted along the aortic wall.** ***Right,*** **corresponding longitudinal anatomic section of the descending aorta. The aortic arch is seen to the right of the photograph in cross section.**

planes, the views obtained from the 2 transducers will be derived from acoustic windows at different levels in the esophagus. As a result, the 2 planes may not be orthogonal. Furthermore, contact between the esophagus and the proximal long-axis imaging surface can be difficult to maintain. To display the biplane images on the same screen, cine-loop split screen display is used. This takes time to perform and, more important, the display of both views is not in real time.

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Circadian Fluctuations in Ventricular Response to Atrial Fibrillation

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The ability of living organisms to synchronize their physiologic functions with the environment has been recognized since the first observations by de Mairan.[1] Renewed interest in circadian aspects of cardiovascular function was sparked by the observation of Muller et al[2] that acute myocardial infarction has a higher incidence during the morning hours. Subsequent studies have confirmed and extended this finding. For example, the incidence of sudden cardiac death,[3] the prevalence of ventricular arrhythmia[4] and myocardial ischemia,[5] as well as platelet aggregability increase in the morning and decline at night. Whereas diurnal variations in sinus rate can be readily examined, direct long-term monitoring of the function of the atrioventricular (AV) node is not feasible with current technology. However, in atrial fibrillation the ventricular response (VR) is determined in part by the refractoriness of the AV node. The purpose of this study was to examine diurnal variations in AV nodal refractoriness in patients with chronic atrial fibrillation.

All ambulatory electrocardiograms recorded at our institutions between 1986 and 1988 were screened for chronic atrial fibrillation. To eliminate the influence of the hospital environment on sleep patterns, in-hospital recordings were not included. Recordings with intermittent sinus rhythm or during therapy with β-blocking agents were also excluded. The study population comprised 63 patients (58 men, 5 women, mean age 68 years) with 63 ambulatory electrocardiograms. Coronary artery disease was diagnosed in 19 patients, valvular heart disease in 14, congestive cardiomyopathy in 6 and systemic hypertension in 4, whereas no heart disease could be identified in 20 patients. This group was compared with 60 patients (58 men, 2 women, mean age 66 years) who were in sinus rhythm. Twenty-three patients had coronary artery disease, 13 hypertension, 1 congestive cardiomyopathy, 1 valvular heart disease, and 22 patients had no history of heart disease. The mean recording duration was 23 ± 2 (14 to 24) hours and 23 ± 1 (18 to 25) hours, respectively.

For each hour, the mean VR was normalized according to the following formula:

$$VR_{(n)} = \frac{VR_{(i)} - VR_{(mean)}}{VR_{(mean)}} \times 100$$

where $VR_{(n)}$ = normalized VR, $VR_{(mean)}$ = mean VR during the 24 hour period, and $VR_{(i)}$ = VR for a given hour(i). In addition, treatment with cardioactive drugs was entered into a database for further analysis. The pooled data were fitted to the following 2-harmonic regression equation (SYSTAT Inc., Evanston, Illinois) to model the nonlinear behavior of heart rate during the 24-hour period:

$$VR_{(i)} = A - B \times \cos\left(2\pi \times \frac{hour_{(i)}}{24}\right) - C \times \sin\left(2\pi \times \frac{hour_{(i)}}{24}\right) + D \times \cos\left(4\pi \times \frac{hour_{(i)}}{24}\right) - E \times \sin\left(4\pi \times \frac{hour_{(i)}}{24}\right)$$

The goodness of fit was tested with an F test. The amplitude of the diurnal variation was defined as the absolute difference between the peak and trough heart rate. Serial autocorrelation analysis was used to detect periodicities in individual as well as pooled heart rate data of each group.[6] This is accomplished by evaluating the statistical relation of each hourly heart rate to its successor (i.e., lag = 1 hour), second successor (lag = 2 hours), and so forth. Periodicities are characterized by significant serial correlations. Differences between treatment groups were analyzed by 2-harmonic regression analysis and considered significant if the 95% confidence limits of

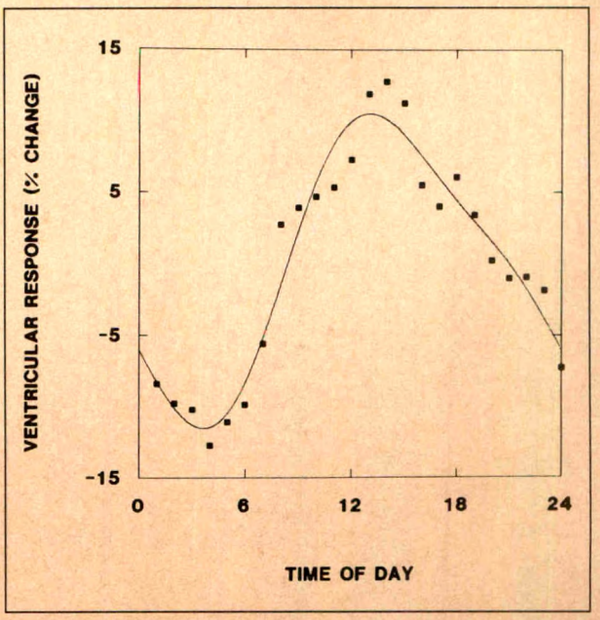


FIGURE 1. Diurnal variation of ventricular response in 82 ambulatory electrocardiographic recordings. Ordinate represents % deviation of hourly rate from 24-hour average. *Solid line*, data fitted to 2-harmonic regression equation.

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the coefficients did not overlap. Data are given as mean ± standard deviation.

The VR revealed a prominent circadian pattern with an estimated peak at 13:01 P.M. *and a trough at 3:40* A.M. *The amplitude of this fluctuation was 22.1% (Figure 1). There was an excellent fit of the data to the regression model ($p < 0.0001$). Autocorrelation analysis of the pooled data also revealed a significant periodicity of the VR up to a lag of 3 hours (1 hour: $r = 0.92$, 2 hours: $r = 0.77$, 3 hours: $r = 0.60$). When the recordings were analyzed individually, the peak VR occurred predominantly during the daytime and the lowest rate at night (Figure 2). First-order autocorrelation coefficients were statistically significant in 41 of the 63 recordings (65%) (mean coefficient 0.52 ± 0.27 [95% confidence interval]) denoting a periodicity in the VR.*

Maintenance therapy with digitalis ($n = 37$) was associated with a lower average VR (84 ± 7 vs 82 ± 6 beats/min, difference not significant). In patients treated with this agent, the peak and trough VR occurred approximately 90 minutes later than in the untreated group.

During sinus rhythm, patients taking digitalis ($n = 11$) had the same daily heart rate as patients not taking this agent (77 ± 5 and 77 ± 5 beats/min, respectively [difference not significant]). Administration of digitalis was associated with a smaller amplitude of the circadian variation (14 vs 19 beats/min), but no susbstantial phase shift.

In the group with sinus rhythm, the diurnal fluctuation of heart rate was characterized by a peak at 11:27 A.M., *a nadir at 2:40* A.M. *and an amplitude of 22.3% (Figure 3). The coefficients of the regression equation did not differ significantly from those calculated for atrial fibrillation (Table I). Autocorrelation of the pooled results disclosed a periodicity for a lag of 1, 2 and 3 hours ($r = 0.93$, 0.77 and 0.55, respectively). Heart rates were usually higher in the late morning and lowest between midnight and 7* A.M. *(Figure 4). In 51 of 60 recordings (85%), first-order autocorrelation coefficients were statistically significant (mean coefficient of 0.64 ± 0.39).*

Diurnal heart rate variations result from modulation of sinus node activity by the autonomic nervous system. Although the AV node is under autonomic control,[7] little is known about its diurnal behavior. The present investigation demonstrates a distinct circadian pattern of the VR which closely follows that of sinus rhythm. These changes are most likely mediated through modulation of AV nodal refractoriness by the autonomic nervous system. This is supported by the study of Billette et al[8] who reported a correlation between the shortest RR interval during atrial fibrillation and the functional refractory period of the AV junction. A similar relation to the refractory period of the accessory pathway has been described in patients with Wolff-Parkinson-White syndrome. Further evidence for a central role of the autonomic nervous system comes from the finding that the maxima and minima of the VR occur at similar times as other cardiovascular events,[2–5] strongly suggesting a common physiologic mechanism. Specifically, the nadir of the VR coincides with high parasympathetic and low sympathetic tone prevailing at night.[9] By contrast, sympathetic discharge surges in the morning, resulting in a shortened refractory period of the AV junction and enhanced transmission of fibrillatory impulses. These data agree well with direct serial measurements of AV node refractory periods by Cinca et al.[10] Between midnight and 7 A.M., these investigators found a significant prolongation of the effective refractory period of the AV node,

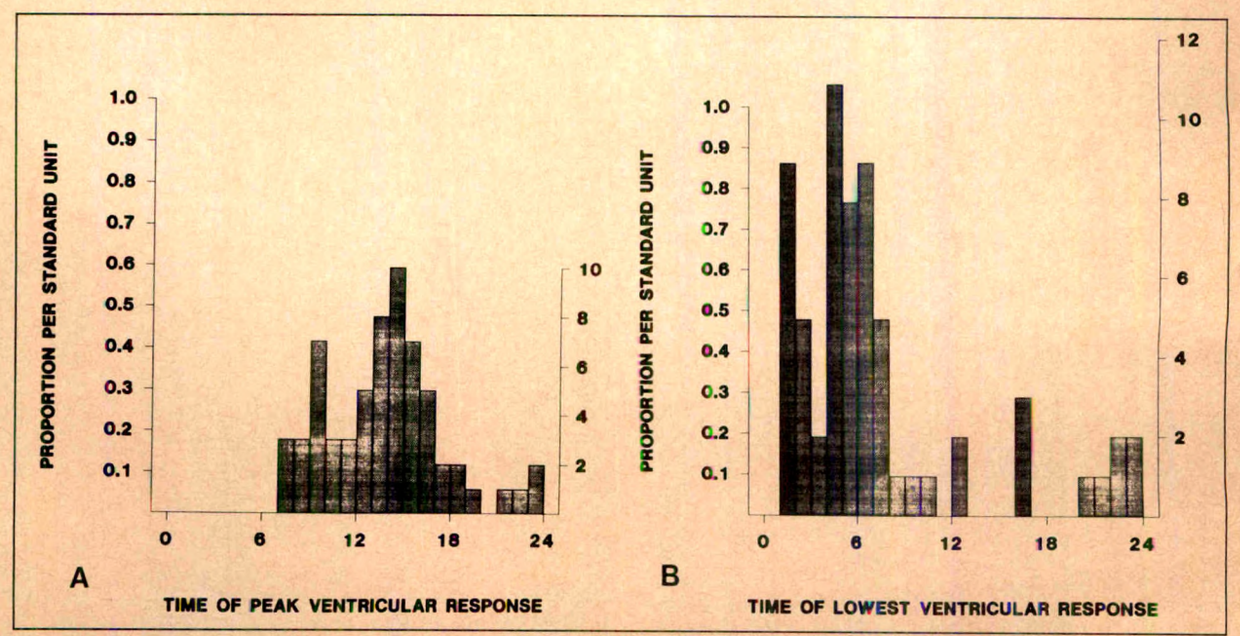


FIGURE 2. Histogram of the times of peak (*A*) and trough (*B*) ventricular response (VR). Note that in most of the patients the highest VR occurred during the daytime with a peak in midmorning and midafternoon. In contrast, the lowest VR is most frequently recorded at night. *Abscissa*, time of day; *ordinate*, number of cases in each hour divided by sample standard deviation.

TABLE I Coefficients of Two-Harmonic Regression Analysis

	Atrial Fibrillation			Sinus Rhythm		
Coefficient	Estimate	95% CI		Estimate	95% CI	
A	0	−0.86	0.86	0	−0.78	0.78
B	8.02	6.80	9.24	8.66	7.56	9.76
C	6.36	5.14	7.58	5.45	4.35	6.55
D	1.95	0.73	3.17	0.06	−1.04	1.16
E	1.15	−0.07	2.37	3.43	2.33	4.53

95% CI = 95% confidence interval.

which they attributed to heightened parasympathetic tone. Moreover, it has been shown in animal experiments that vagal stimulation prolongs AV conduction, whereas sympathetic stimulation shortens it.[11,12]

Although the data for sinus rhythm and atrial fibrillation stem from different patient populations, the response of the sinoatrial and AV nodes to diurnal influences is remarkably similar (Table I). The closely matched diurnal heart rate patterns can thus be viewed as a manifestation of the integration of the sinoatrial and AV nodes. This is also suggested by animal experiments performed by O'Toole et al.[7] In a study of the baroreceptor control of sinoatrial rate and AV conduction in anesthetized dogs, they found that increments in arterial pressure mediated through the vagal efferent limb of baroreflexes elicited a parallel chronotropic and dromotropic response that preserved 1:1 AV conduction. However, when the chronotropic response to arterial pressure stimuli was prevented by atrial pacing, the independent vagal slowing of anterograde AV conduction resulted in high-degree AV block.

The influence of β blockers and digitalis on the VR and its circadian variation appears to be relatively modest. This may at least in part be due to selection bias since the VR of patients not deemed to require rate control is likely to be moderate. Further studies are needed to clarify the influence of these drugs on the diurnal pattern of the VR.

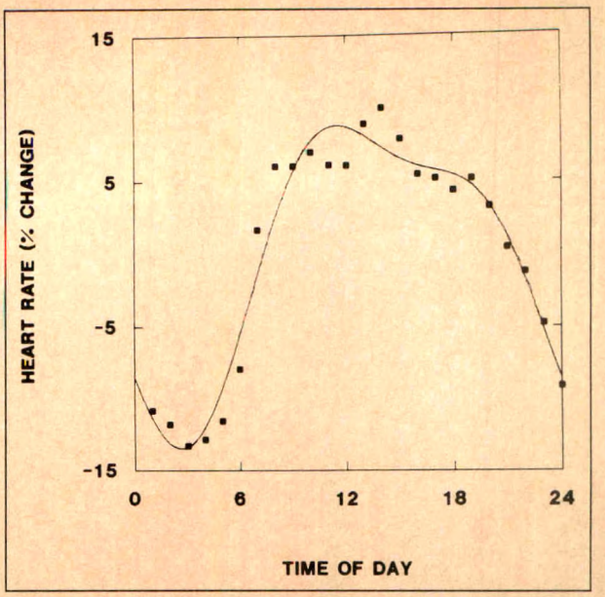


FIGURE 3. Diurnal variation of heart rate during sinus rhythm from 78 Holter recordings. *Solid line*, data fitted to 2-harmonic regression equation.

It is concluded that the results of the present study are consistent with a primary role of the autonomic nervous system in circadian changes of AV nodal function.

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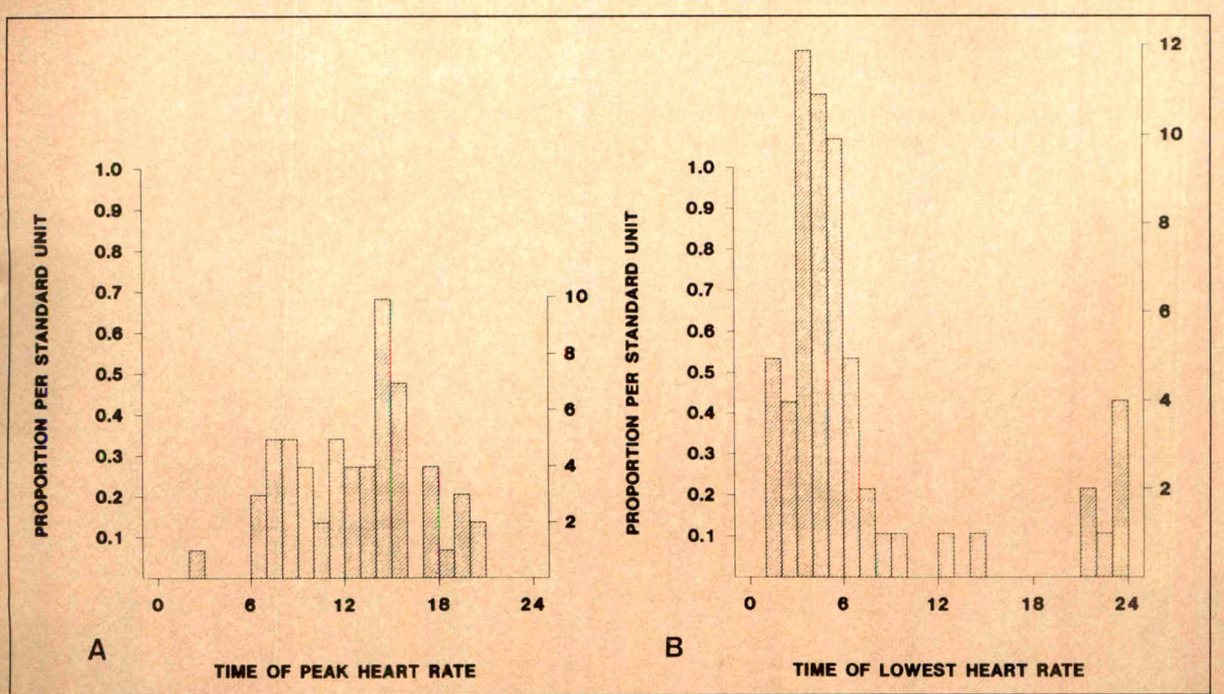


FIGURE 4. Histogram of times of peak (*A*) and trough (*B*) heart rate. For explanation, see Figure 2.

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Comparison of Indications for Aortic Valve Replacement in 1978 and in 1988

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Aortic valve diseases constitute the majority of valvular heart diseases requiring valve replacement in the United States. During the past 3 decades, surgical replacement of the aortic valve has become the treatment of choice for a variety of aortic valve diseases.[1] The etiologies of aortic valvular lesions requiring surgery have also changed considerably over the past several decades. For instance, with the decreasing incidence of clinical acute rheumatic fever in the western world, a decline in postinflammatory aortic stenosis (AS) has already been observed based on pathologic studies.[2,3] Concomitantly, there has been a gradual increase in the number of patients with degenerative calcific AS undergoing valve replacement.[4] This retrospective study was undertaken to determine changes in the clinical indications leading to aortic valve replacement and the etiologies of underlying valvular pathology in a university hospital in 1978 and 1988.

The charts of all patients who underwent aortic valve replacement at Moffitt-Long Hospital during the years 1978 and 1988 were reviewed. Moffitt-Long Hospital is a referral university hospital drawing patients from northern California. During the study periods, the majority of patients requiring open-heart surgery at San Francisco General Hospital had been transferred to Moffitt-Long Hospital. San Francisco General Hospital does not have a cardiac surgery program and serves as the primary health care provider for the indigent population of San Francisco County.

The following 5 categories of clinical indications for valvular surgery were identified: (1) AS, (2) chronic aortic regurgitation (AR), (3) acute AR, (4) AS/AR, and (5) infective endocarditis refractory to medical therapy. All patients were classified under 1 of these clinical indications. The age of patients undergoing aortic valve replacement was also recorded.

Based on historical, clinical, echocardiographic, cardiac catheterization, intraoperative and pathologic findings, the etiology of the valvular pathology was determined. If all of the specific requirements of each etiologic class could not be met, the etiology was considered unknown. The specific criteria used are listed in Table I.

The presence of significant coronary artery disease in patients with AS requiring valve replacement who had undergone coronary arteriography was recorded. Significant coronary artery disease was defined as a >50% reduction in the diameter of ≥1 coronary arteries on coronary arteriogram. The interpretation of electrocardiograms of patients with AS was also reviewed.

Fisher's exact test was used to compare the number of patients with chronic aortic insufficiency who underwent aortic valve replacement in 1978 and 1988.

The number of patients undergoing aortic valve replacement at this institution was 63 and 39, during the years 1978 and 1988, respectively. The median age was 62 years in 1978 and 64 years in 1988.

AS was the most common clinical indication for aortic valve replacement, accounting for 49% of such replacements in 1978 and 67% in 1988. The other clinical indications in descending order were the following: chronic AR, AS/AR, acute AR, and infective endocarditis refractory to medical therapy. The proportion of patients with AS/AR, acute AR and refractory infective endocarditis who underwent aortic valve replacement remained essentially constant over the decade. The percentage of patients with chronic AR requiring valvular surgery decreased from 32% in 1978 to 13% in 1988.

The 2 most common etiologies of AS were degenerative calcification of the tricuspid semilunar aortic valve and calcification of congenitally abnormal valve. Degenerative calcification of the tricuspid aortic valve was the cause of AS in 42 and 46% of patients in 1978 and 1988,

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TABLE I Criteria for the Etiology of Valvular Pathology Leading to Aortic Valve Replacement

- Aortic stenosis with or without aortic regurgitation
  - Degenerative aortic stenosis
    - Age >56 yrs[2]
    - Presence of 3 unfused leaflets
    - Lack of mitral stenosis
    - Calcium in cusps without significant commissural fusion
  - Congenital aortic valvular stenosis
    - Bicuspid, unicuspid or acommissural aortic valve based on intraoperative or pathologic findings
    - Lack of mitral stenosis
  - Postinflammatory
    - Presence of mitral stenosis
    - Intraoperative findings of significant commissural fusion and fibrosing distortion of the valve and the chordae
- Chronic aortic regurgitation
  - Postinflammatory
    - Presence of mitral stenosis
    - Intraoperative findings of significant fibrosing distortion of the valve
    - Lack of significant aortic root dilation (<6.0 cm)
  - Aortic root dilation
    - Abnormal dilation of the aortic root (>6.0 cm by echocardiogram and/or catheterization) causing valvular regurgitation
  - Congenital aortic valvular regurgitation
    - Bicuspid aortic valve or congenital fenestration based on the intraoperative report or pathologic findings
    - Lack of mitral stenosis
    - Lack of significant aortic root dilation (<6.0 cm)
  - Infective endocarditis
    - History of infective endocarditis with subsequent aortic regurgitation for >6 months
    - Lack of mitral stenosis
    - Lack of significant aortic root dilation (<6.0 cm)
  - Other causes of aortic regurgitation: membraneous subvalvular stenosis, ventricular septal defect
- Acute aortic regurgitation
  - Infective endocarditis
    - Recent history of infective endocarditis
    - Hemodynamic instability as a result of valvular insufficiency
    - Presence of vegetations on the aortic valve or cusp perforation resulting in aortic valvular insufficiency
    - Presence of acute inflammatory cells on histologic evaluation of the valve
- Infective endocarditis refractory to medical therapy
  - Hemodynamically stable endocarditis unresponsive to medical therapy

respectively. Congenital etiologies (bicuspid and other congenital valvular lesions) accounted for 42% of AS patients in 1978 and for 42% in 1988. The third most frequent cause of AS in the 2 study years was postinflammatory calcification of the aortic valve. The median age of patients undergoing aortic valve replacement for AS was 69 and 71.5 in 1978 and 1988, respectively.

Chronic AR was most often caused by postinflammatory valvulitis and aortic root dilation in 1978 (Table II). Among the 5 patients with chronic AR in 1988, no single etiology was dominant. One patient in 1978 had chronic AR as a result of ventricular septal defect, which was repaired concomitantly with valve replacement. In 1988, 1 patient had developed chronic AR due to surgical aortic valve commissurotomy.

Postinflammatory valve diseases, congenitally abnormal aortic valves and degenerative valve changes were the etiologies of AS/aortic insufficiency in both study years. Infective endocarditis was the sole etiology of acute AR in patients needing aortic valve replacement in 1978 and 1988 (Table II).

Additionally, 3 patients underwent aortic valve replacement for infective endocarditis refractory to medical therapy during the 2 study years. In 1978, 1 patient had fungal endocarditis with recurrent embolic events. In 1988, 1 patient had aortic ring abscess with impingement on the conduction system; the other patient had persistently positive blood cultures despite an adequate trial of medical treatment.

Among the 31 patients with AS in 1978, 26 underwent coronary arteriography and, of these, 11 (42%) had significant coronary artery disease that warranted bypass grafting. In 1988, 23 of the 26 patients with AS underwent coronary arteriography, and of these 7 (30%)

TABLE II Etiologies of Chronic Aortic Regurgitation, Aortic Stenosis/Regurgitation and Acute Aortic Regurgitation

Etiologies	1978	1988
Chronic aortic regurgitation		
Postinflammatory	8	2
Aortic root dilation	6	0
Infective endocarditis	3	1
Congenital	2	1
Others	1	1
Total	20*	5
Aortic stenosis/regurgitation		
Postinflammatory	3	2
Bicuspid	2	1
Degenerative	3	1
Total	8	4
Acute aortic regurgitation		
Infective endocarditis	3	2

* $p < 0.05$ when compared to 1988.

had significant coronary artery disease that necessitated aortocoronary bypass grafting concomitantly with valve replacement.

Abnormal electrocardiogram was found in 29 of the 31 patients in 1978 and in all of 26 patients in 1988. Left ventricular hypertrophy on electrocardiogram was present in 52% of the patients with AS who required aortic valve replacement in 1978 and in 58% of patients in 1988. As a group, 96% of patients with AS had an abnormal electrocardiogram and 54% had left ventricular hypertrophy pattern.

There were few changes in the clinical indications for aortic valve replacement from 1978 to 1988 based on this study. AS remained the major clinical indication for aortic valve replacement in both study years, accounting for 49% of the aortic valve replacements in 1978 and for 67% in 1988. A notable finding of this study was a dramatic decrease in chronic AR as a clinical indication for aortic valve replacement, from 32% in 1978 to 13% in 1988. The reason for this decrease is unclear. It may be solely due to a change in the pattern of referral to this institution, to a decrease in the total number of patients with chronic AR, or to a reduction in the number of patients with chronic AR who are undergoing valve replacement as a result of improved medical therapy with an attendant delay in referral for surgery.

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Noninvasive Evaluation of Left Ventricular Performance with a New Systolic Time Interval, the Q-V Peak, and Comparison with Established Systolic Time Intervals

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Left ventricular (LV) performance can be evaluated noninvasively by determination of systolic time intervals including the preejection period (PEP) of the left ventricle and the ratio of the LV preejection period/LV ejection time (PEP/LVET).[1–5] To our knowledge, no new systolic time interval with a sufficient potential for predicting LV performance has been widely used clinically since the inception of the PEP and PEP/LVET. In this study we evaluated LV performance using a new systolic time interval obtained by continuous-wave Doppler echocardiography and electrocardiography. In addition, we compared the effectiveness of this new systolic time interval with that of the established time intervals for evaluating left ventricular performance.

We studied a series of 57 patients (43 men and 14 women, average age ± standard deviation 59 ± 8 years) who were undergoing diagnostic cardiac catheterization for the evaluation of coronary artery disease. Heart rates ranged from 51 to 95 beats/min. Patients were excluded if they had valvular heart disease noted on echocardiography, left bundle branch block or atrial fibrillation. Twenty-three patients were diagnosed angiographically as having old myocardial infarction, 20 as angina pectoris and 14 as atypical chest pain. Except for nitroglycerin, all cardiac medications were routinely discontinued in these patients before the study. All patients gave informed consent before initiation of the protocol. Flow velocity wave forms at the ascending aorta were obtained with the patient supine using continuous-wave Doppler echocardiography (Toshiba SSH-65A) with a 2.5-MHz pencil-type transducer from the suprasternal notch. Recordings were obtained on a line-scan recorder at a paper speed of 100 mm/s with lead II electrocardiographic, phonocardiographic and carotid arterial pulse tracings. An acceleration-type heart sound sensor was placed over the aortic area in a position optimal for recording the initial high frequency vibration of the second heart sound. A spygmograph transducer with a piezoelectric device for pulse pickup was placed over the right carotid artery. Recordings were obtained during expiration to a level of functional residual lung capacity. The following phases of the cardiac cycle were measured directly: (1) Q-V peak, measured from the beginning of electrocardiographic Q wave to the peak flow velocity of the ascending aorta; (2) LVET, measured from the beginning upstroke to the trough of the incisura of the carotid arterial pulse tracing; (3) total electromechanical systolic interval (Q-S2), measured from the onset of the electrocardiographic Q wave to the first high frequency vibrations of the aortic component of the second heart sound; and (4) RR interval (Figure 1). These intervals were measured for 5 successive cardiac cycles by a cardiologist who did not know the patient history or the re-

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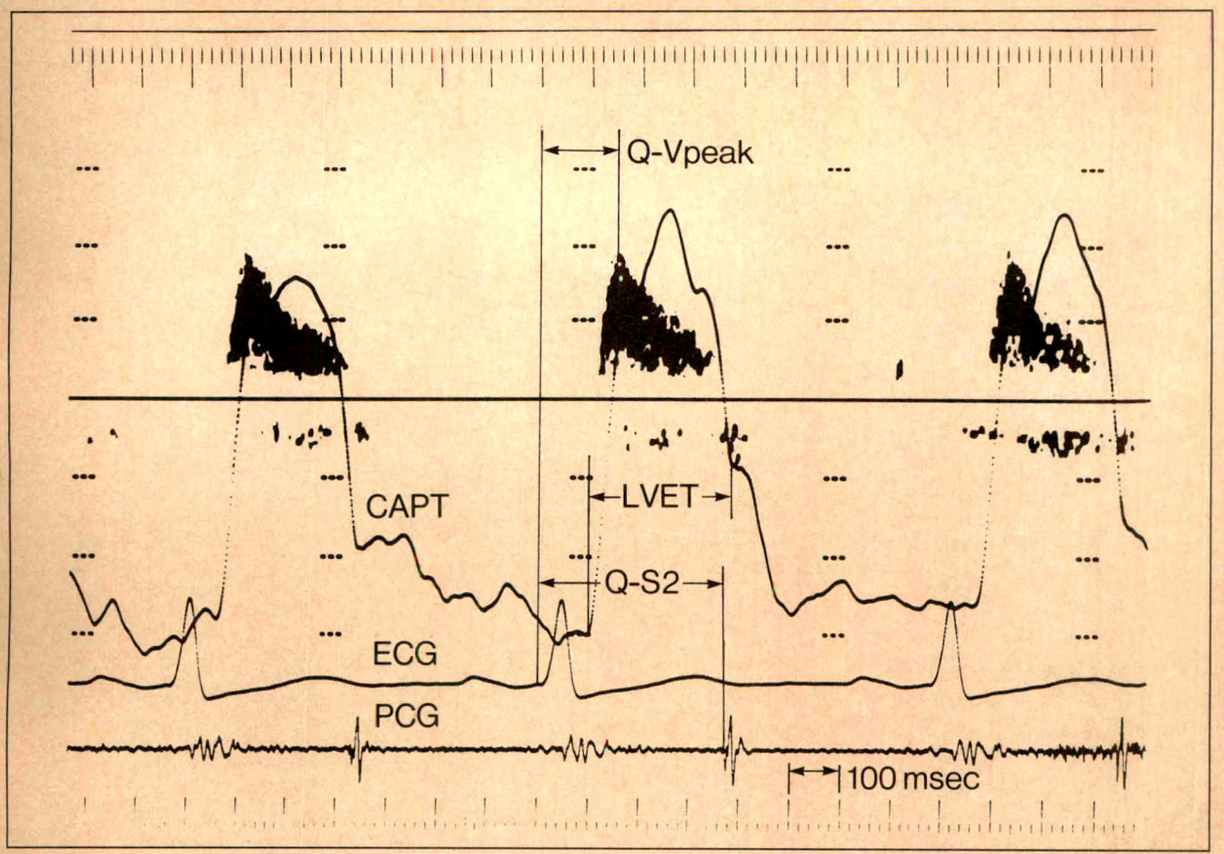


FIGURE 1. Simultaneous recording of flow velocity wave forms at the ascending aorta with continuous-wave Doppler echocardiography, electrocardiography (ECG), phonocardiography (PCG) and carotid arterial pulse tracing. The systolic time intervals Q-V peak, left ventricular ejection time (LVET) and Q-S2 were measured as shown. CAPT = carotid arterial pulse tracing; Q-S2 = total electromechanical systolic interval; Q-V peak = systolic time interval measured from the beginning of electrocardiographic Q wave to the peak flow velocity of the ascending aorta.

sults of other examinations. A mean of 5 cardiac cycles was used as the value for each patient. The following intervals were calculated from those measurements: (1) PEP, derived by subtracting LVET from Q-S2 interval; (2) PEP/LVET, derived from dividing PEP by LVET; (3) Q-V peak/$\sqrt{RR}$, obtained by dividing Q-V peak interval by square root of the RR interval, to correct for the effect of heart rate. All patients underwent cardiac catheterization within 2 hours of the noninvasive measurements. Biplane contrast ventriculography was performed and LV ejection fraction (LVEF) was calculated by the area-length method. Correlations between Q-V peak, Q-V peak/$\sqrt{RR}$, PEP, PEP/LVET and LVEF were evaluated using linear regression analysis. The relation between Q-V peak and LVEF is shown in Figure 2. Q-V peak values ranged from 130 to 230 ms. A highly significant negative correlation was observed between Q-V peak and LVEF ($r = -0.80$, $p < 0.001$). To correct for the effect of heart rate, Q-V peak was divided by the square root of the RR interval. The correlation between Q-V peak/$\sqrt{RR}$ and LVEF was $r = -0.74$, highly significant ($p < 0.001$); however, the correlation coefficient was lower than before the correction was made for heart rate. The relation between PEP and LVEF is shown in Figure 3. PEP, which ranged from 70 to 140 ms, showed a significant negative correlation with LVEF ($p < 0.001$); however, the correlation coefficient ($r = -0.69$) was lower than that of the Q-V peak and LVEF. The relation between the PEP/LVET and LVEF is shown in Figure 4. The LVET values ranged from 240 to 320 ms and the calculated PEP/LVET ranged from 0.24 to 0.52. The

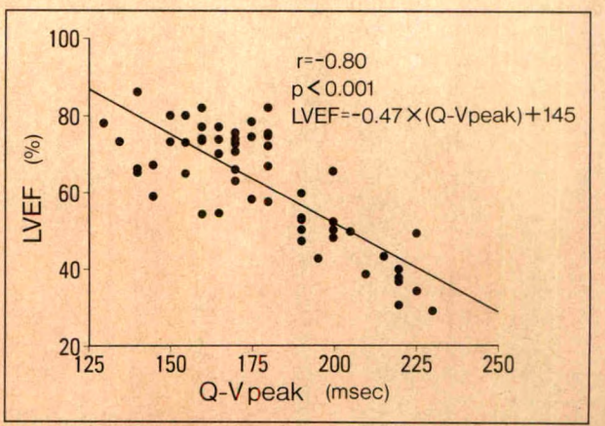


FIGURE 2. Relation between the Q-V peak and left ventricular ejection fraction (LVEF). The Q-V peak shows a significant negative correlation with left ventricular ejection fraction.

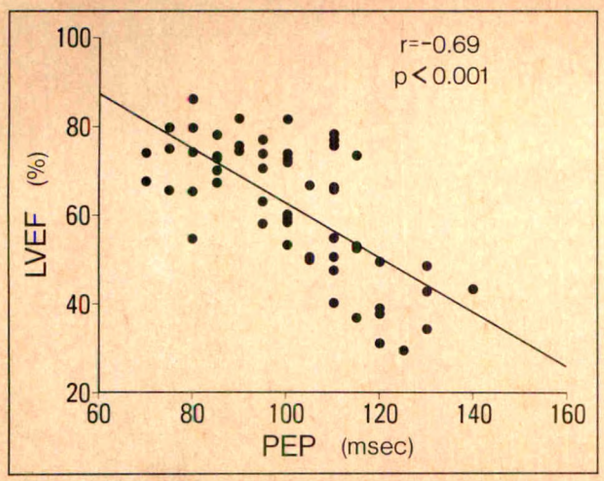


FIGURE 3. Relation between the preejection period (PEP) and left ventricular ejection fraction (LVEF). PEP shows a significant negative correlation with LVEF; however, the correlation coefficient was lower than that between the Q-V peak and LVEF.

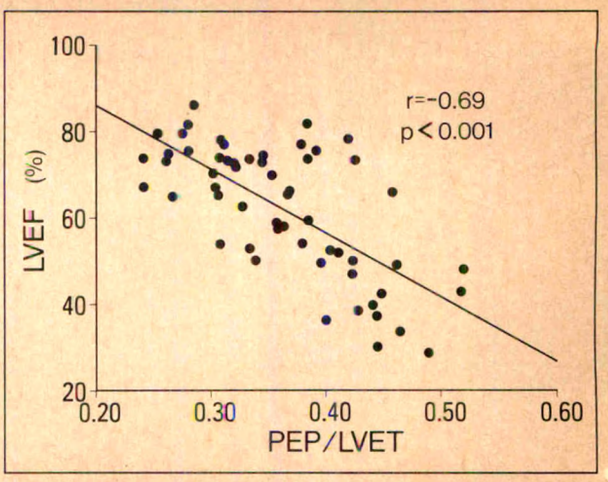


FIGURE 4. Relation between the preejection period/left ventricular ejection time (PEP/LVET) and left ventricular ejection fraction (LVEF). PEP/LVET shows a significant negative correlation with LVEF; however, the correlation coefficient was lower than that between the Q-V peak and LVEF.

correlation between the PEP/LVET and LVEF was significant ($p < 0.001$), but the correlation coefficient $r = -0.69$ was also lower than that between the Q-V peak and LVEF.

Although noninvasive and quantitative evaluation of LV performance at the patient's bedside is important, it is inconvenient. Such systolic time intervals as PEP and PEP/LVET have been used for this purpose.[1–5] We evaluated LV performance using a new systolic time interval obtained from the simultaneous recording of continuous-wave Doppler echocardiography and electrocardiography. We then determined whether any systolic time interval would be superior for predicting LVEF, comparing Q-V peak with established systolic time intervals, i.e., PEP or PEP/LVET.

Q-V peak is composed of PEP and the acceleration phase of aortic blood flow in systole. Many previous reports have shown that PEP lengthens with impaired LV performance[1–5]; our study also demonstrated this finding. It has been reported that the acceleration rate of the aortic ejection flow declines with a deterioration in LV performance.[6–10] From this observation the acceleration time of aortic ejection flow is considered to lengthen with a reduction in LV performance. We therefore considered that the Q-V peak interval, which is the sum of PEP and the acceleration time of the aortic ejection flow, could potentially predict LV performance more effectively than PEP. Our results showed that Q-V peak is more closely correlated with LVEF than are either PEP or PEP/LVET. Q-V peak/$\sqrt{RR}$ also correlated well with the LVEF, but again, the correlation coefficient was lower than that between Q-V peak and LVEF. We consider that the heart rate did not affect the Q-V peak interval to any appreciable extent, because no patient in this study had marked tachycardia or bradycardia.

Currently M-mode and 2-dimensional echocardiography are used routinely for evaluating LV performance in patients with heart disease. However, these methods are less useful for quantitating LV performance in patients with coronary artery disease because their left ventricles often show abnormal wall motion. In such patients, we can predict the LVEF with the Q-V peak. We can now obtain this information at the patient's bedside by performing continuous-wave Doppler echocardiography immediately after 2-dimensional echocardiography.

We conclude that one can conveniently evaluate LV performance noninvasively using the Q-V peak as the systolic time interval in patients with chronic coronary artery disease and atypical chest pain. Q-V peak was more closely correlated with LVEF than were either of the established systolic time intervals, PEP and PEP/LVET.

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CASE REPORT

Selective Infusion of Thrombolytic Therapy in the Acute Myocardial Infarct-Related Coronary Artery as an Alternative to Rescue Percutaneous Transluminal Coronary Angioplasty

Paul A. Gurbel, MD, Charles J. Davidson, MD, E. Magnus Ohman, MD, Jack E. Smith, MD, and Richard S. Stack, MD

The management of patients with acute myocardial infarction in whom reperfusion has been unsuccessful with standard dose thrombolytic therapy remains controversial.[1] Rescue percutaneous transluminal coronary angioplasty (PTCA) has been associated with a high reocclusion rate after failed intravenous tissue plasminogen activator (TPA) with accompanying high morbidity and mortality.[2] It has been postulated that PTCA in the setting of thrombolytic therapy may induce subintimal hemorrhage, which may lead to reocclusion.[3] As an alternative method for restoring coronary patency after failed intravenous TPA, we describe the results of selective intracoronary injection of a longer acting thrombolytic agent, without adjunctive PTCA, using an infusion catheter that provides a mechanical jet effect to disrupt the coronary thrombus. Use of this coronary thrombolytic technique was successful in each patient after failed intravenous TPA.

Patient 1 was a 46-year-old man who developed substernal chest pain 2 hours after using intravenous cocaine. He was treated with a total of 100 mg of TPA intravenously at a local hospital approximately 3 hours after the onset of chest pain. The patient was transported to Duke Medical Center and taken to the interventional laboratory for further study because of persistent chest pain and ST-segment elevation. Coronary angiograms showed a 100% occlusion in the proximal right coronary artery. Biplane ventriculography showed severe inferior akinesia and an ejection fraction of 56%. A 0.014-inch High Torque Intermediate™ coronary guidewire (Advanced Cardiovascular Systems) was advanced through an 8Fr Judkins right coronary guide catheter (Interventional Medical, Inc.) to a position just proximal to the total occlusion. Over this guidewire, a Tracker-18 Hi-Flow™ catheter (Target Therapeutics) was advanced immediately proximal to the occlusion. The guidewire was retracted approximately 10 cm inside the catheter.

Urokinase (500,000 U in 10 ml sterile water) was delivered in 2-ml boluses over 10 minutes through the Tracker catheter into the area of thrombus. Repeat angiograms, 10 minutes after the final bolus, showed restoration of patency with Thrombolysis in Myocardial Infarction (TIMI) trial grade 3 flow and a residual 75% occlusion. After 7 days of intravenous heparin therapy, there was a residual 75% stenosis in the proximal right coronary artery and the ejection fraction was 42%. The patient underwent successful PTCA.

Patient 2 was a 74-year-old woman who developed recurrent chest pain and ST-segment elevation 24 hours after receiving intravenous TPA and heparin therapy for an acute myocardial infarction. Coronary angiography showed a 100% proximal right coronary artery occlusion. Patency and normal flow in the infarct-related artery was successfully restored with a residual 95% lesion using the same technique as in patient 1. After 2 days of heparin therapy, the patient developed chest pain and 1-mm ST elevation on her electrocardiogram 4 hours after sheath removal and a vasovagal episode. Repeat catheterization showed a 95% proximal right coronary artery stenosis with TIMI grade 3 flow. The patient underwent successful PTCA via an over-the-wire technique and was discharged without any further event.

Patient 3 was a 52-year-old man who presented to his local hospital with an acute anterior myocardial infarction and was administered intravenous TPA (100 mg) starting 2.5 hours after onset of symptoms. He was transferred due to persistent chest pain and 3-mm ST elevation in the precordial leads. Cardiac catheterization showed a 100% occlusion in the proximal left anterior descending artery (Figure 1) and an ejection fraction of 47%. An 8Fr

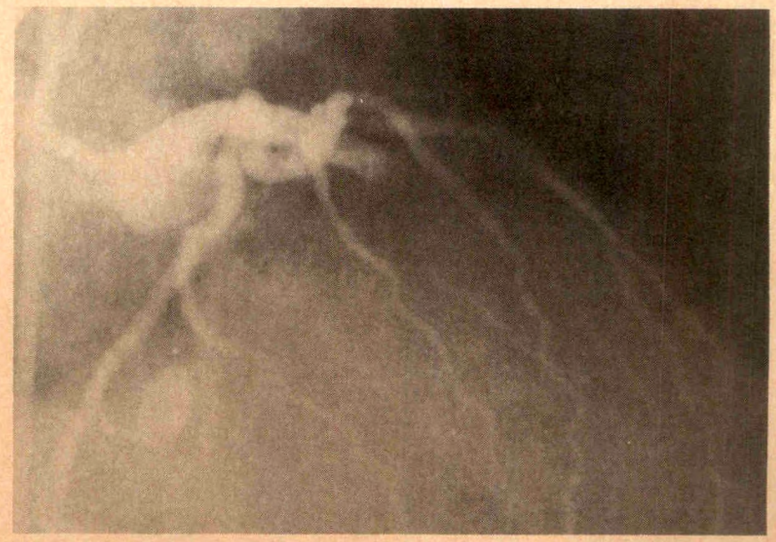


FIGURE 1. Total occlusion of proximal left anterior descending artery.

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guide catheter was inserted into the left coronary artery, through which the 0.014 coronary guidewire and Tracker-18 Hi-Flow™ catheter were advanced into the left anterior descending artery just proximal to the obstruction (Figure 2). Intracoronary urokinase was infused with reduction of the obstruction to 25% and restoration of TIMI grade 3 flow (Figure 3). An intraaortic balloon was placed for persistent hypotension. Repeat cardiac catheterization after 7 days of heparin therapy showed a 25% obstruction in the left anterior descending artery and an ejection fraction of 46%.

Patient 4 was a 48-year-old man who was admitted in cardiogenic shock to a local hospital 30 minutes after the onset of chest pain. Electrocardiogram showed an acute inferior and right ventricular infarction. He was treated with 100 mg intravenous TPA and transferred. On arrival, 4 hours after the onset of symptoms, he remained hypotensive with persistent ST-segment changes. Cardiac catheterization showed a 100% proximal right coronary artery occlusion; the ejection fraction was 41%. Right-sided cardiac catheterization confirmed right ventricular infarct hemodynamics. The Tracker-18 Hi-Flow™ catheter was inserted into the proximal right coronary artery just before the occlusion and urokinase was infused as in cases 1 and 2. Repeat angiograms showed TIMI grade 2 flow with extensive filling defects throughout the vessel. The previous proximal 100% obstruction was now 75%. PTCA of the 75% stenosis failed to improve flow despite reduction of this lesion to a minor irregularity. The patient remained in cardiogenic shock in the coronary care unit. Two-dimensional echocardiography showed a severely hypocontractile right ventricle and inferior wall of the left ventricle. Despite aggressive vasopressor support, the patient died 48 hours after admission.

Information on the success of further intracoronary thrombolytic therapy after failed intravenous therapy is limited.[4,5] Data from our institution in 46 patients with a totally occluded coronary artery in whom intravenous TPA was unsuccessful indicate that 56% of these patients had coronary artery patency restored after infusion of urokinase through a coronary guide catheter (unpublished data). In the Thrombolysis and Angioplasty in Myocardial Infarction-1 (TAMI-1) trial, rescue PTCA had a complete success rate (<50% residual stenosis) of 73% and was complicated by a high reocclusion rate of 29%.[2] In the event of failure to establish reperfusion with PTCA, there is an exceedingly high mortality rate of 44%.[2] In contrast, in the TAMI-2 trial, which used intravenous urokinase and TPA for the treatment of acute myocardial infarction, the reocclusion rate of rescue PTCA was only 4%. This suggests that prior urokinase therapy may favorably affect reocclusion.[6]

Based on the TAMI trial data on reocclusion and the evidence that intracoronary urokinase is associated with less bleeding complications than intracoronary streptokinase,[7] intracoronary urokinase infusion was chosen to restore coronary patency. The efficacy of the selective injection of urokinase directly into coronary thrombus using a new infusion catheter technique is shown in 4 patients with acute myocardial infarction. It is postulated that establishment of reperfusion without the use of PTCA may cause less vessel trauma and hence a lower incidence of reocclusion and further complications. Before inserting this catheter, we showed that 2-ml bolus injections of saline solution through the catheter with a 0.014-inch wire in its lumen provided a jet-like spray to exit its distal tip. This jet could provide a mechanical effect that facilitates the dissolution of thrombus by thrombolytic agents without significantly adding trauma to the vessel wall. Erbel[7] described a reperfusion technique in which a guidewire is first passed through the coronary thrombus and is followed by slow infusion of intracoronary streptokinase through a selective catheter. This method restored flow in 80% of patients in whom intravenous streptokinase was unsuccessful. Our technique differs by avoiding passage of a guidewire that could traumatize a ruptured plaque and embolize thrombus. We also deliver the thrombolytic agent in boluses instead of slow infusion, which may enhance its effect. Although intracoronary urokinase has been shown to restore patency in 60% of patients with acute

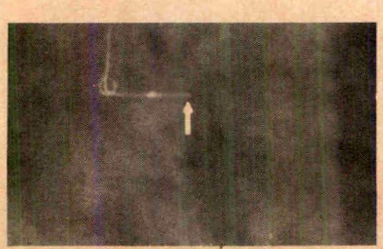


FIGURE 2. Tracker-18 Hi-Flow™ catheter in proximal left anterior descending artery being inserted over guidewire (*arrow*).

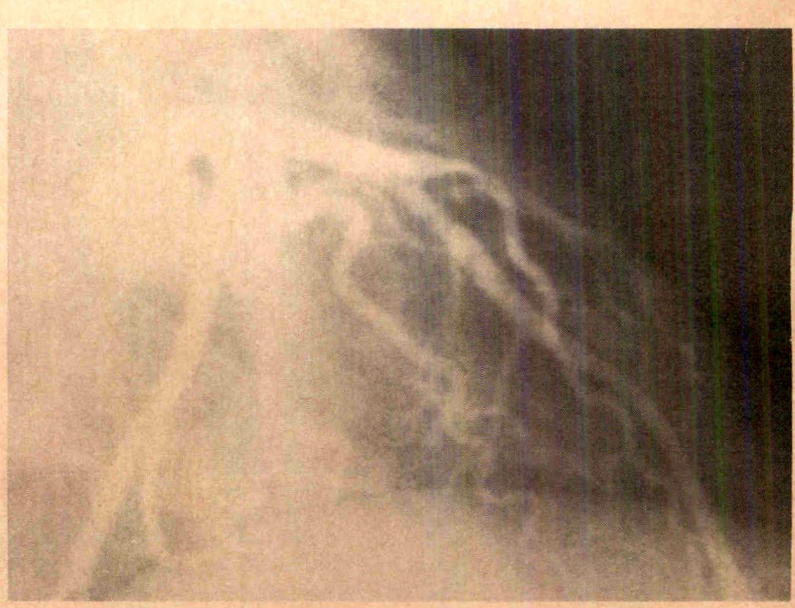


FIGURE 3. Restoration of flow with residual 25% proximal stenosis.

myocardial infarction when infused slowly through a standard coronary catheter,[8] our technique successfully restored coronary flow in each case. In the event that it does not suitably restore blood flow, it may disrupt the thrombus enough to facilitate the passage of a guidewire for PTCA.

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Assessing Left Ventricular Ejection Force

Recently Isaaz et al[1] reported on the assessment of left ventricular ejection force using a method based on Newton's second law of motion (force = mass × acceleration). To *approximate* this equation they have taken the total mass ejected during the acceleration phase, derived from the integral of the aortic flow velocity signal, and multiplied it by the mean acceleration during this phase. This approach entails the digitization of the velocity curve prior to integration, the resulting force calculated indeed showing a strong correlation with cardiac condition. As the flow curve has already been digitized, this approximation can be completely avoided with no extra effort as follows.[2]

First, with regard to blood flowing from the left ventricle, the mass term in Newton's second law is continuously changing; thus, an alternative form of equation is necessary. This is generally phrased as Force = rate of change of momentum and implies for the analysis given by Isaaz (using his notation): Mean ejection force averaged over the acceleration period (0 − t) equals, $\rho \times CSA \times \int_0^t v^2dt \times 1/t$, where the term under the integral sign is now the instantaneous blood velocity *squared*. Second, as the digitized values of the velocity time trace are already available, it is a simple task for the computer program to square these values before integration. If this expression is applied to a velocity curve of the form of Figure 1 in Isaaz[1] (an approximately triangular wave form), then the new value is about 33% lower; if applied to Figure 2 (approximately part of a sine wave), the new result is 20% smaller, namely 24 kdynes. Two further points can be made.

(1) The aforementioned analysis refers to only the "out-component" as described by Isaaz.[1] The "in-component" consisting of accelerations within the ventricle can be expressed as a term involving the changing shape of the ventricle (shape factor I) and the end-diastolic volume, both indeed difficult to assess. Taking an approximate case where I = 0.1, a constant, with a sine curve velocity profile, this second term would be 15.5 kdynes, more than half that of the "out-component" term.

(2) Although outside the scope of the *ejection* force analysis, it is worth pointing out that to cause ejection in the first instance[2] the pressure in the ventricle must be increased to end-diastolic pressure (EDP) and above. This requires forces in the ventricle several times larger than those discussed above. Approximate calculations show that during isovolumic contraction, the total force achieved by the heart is typically 4,000 kdynes (nominally calculated as EDP × CSA of heart).

To conclude, with the data already available from velocity profiles, an *exact* calculation of the mean force produced by ejection of blood during the acceleration phase ("out-component") can be obtained by a simple adjustment to the calculation procedure in Isaaz.[1]

Philip A. Arundel, PhD
Alderley Park, United Kingdom
4 December 1989

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REPLY: In our article we used the *system formulation* for estimating the mean ejection force imparted to the aortic blood in early systole. In this study, the mean ejection force was defined as the product of the mass of blood ejected during acceleration time with its mean local acceleration. This mathematical model for estimating the ejection force has been proposed previously by other investigators (reference 4 of our article). Our data showed that mean ejection force calculated using this model is a good index of global left ventricular performance. However, as Arundel says and as we wrote in our article, this model provides only an attempt at evaluating a fraction of the forces that act to cause ejection. A more complete approach would include the calculation of the force involved in the acceleration of the ventricular blood mass ("in-component"). The *control-volume formulation* is another method of description of fluid mechanics problems that allows us to apply basic laws of motion (as Newton's second law) when the mass is changing. Using the control-volume formulation, it is possible to derive a more complex expression of the ejection force based on the generalized linear momentum equation applied to the left ventricular/aortic coupling. The details of the different mathematical models for noninvasive calculation of the ejection force using the system formulation as well as the control-volume formulation have been described elsewhere.[1] If we use the control-volume formulation, the total mean ejection force (in-component + out-component) averaged over the acceleration period (0 − t) is calculated as $F_{mean} = 1/t \int_0^t F_i dt$, where F_i is the total instantaneous ejection force[1] and the "out-component" of the mean ejection force can be expressed as: $(1 - k) \times \rho \times CSA \times 1/t \int_0^t v^2dt$[1], where k is a geometric factor. In the physiological range of aortic and ventricular dimensions, k ranges from 0.14 to 0.06 (Isaaz et al, unpublished data). Thus, 1 − k is close to the unity and the out-component of the mean ejection force can be simplified as $\rho \times CSA \times 1/t \int_0^t v^2dt$ — that is, the expression proposed by Arundel. In a series of 19 patients, the average value for the out-component of the mean ejection force calculated as $\rho \times CSA \times 1/t \int_0^t v^2dt$ was 21% lower than that obtained from the method described in our article. However, despite this difference in absolute values, there was a high linear correlation between both expressions (r = 0.99, p = 0.0001, intercept = 0.27, slope = 1.25, SEE = 0.91). This close linear correlation between both expressions suggests that no improvement may be expected using $\rho \times CSA \times 1/t \int_0^t v^2dt$ for assessing left ventricular performance instead of the formula used in our article.

We agree with Arundel that the total force exerted by the myocardium to accelerate blood out of the ventricle (in-component + out-component) is small when compared to the force required for overcoming the aortic end-diastolic pressure and opening the valve. However, the ejection force is associated with a substantial ventricle-to-aorta pressure gradient at rest,[1,2] which becomes more important during exercise.[2] The total left ventricular systolic load can be separated into an *extrinsic* component associated with the aortic root pressure and an *intrinsic* component associated with the ejection pressure gradient between the left ventricle and the aortic root.[2] Thus, the ventricle-to-aorta pressure gradient contributes significantly to the total left ventricular systolic load and, in particular, cannot be ignored during conditions characterized by vigorous ejection.[2] Therefore, calculation of the total ejection force using Doppler echocardiography[1] is important because it allows us to calculate noninvasively the total left ventricular systolic load throughout the ejection period, providing a more comprehensive noninvasive evaluation of systolic ventricular dynamics.

Karl Isaaz, MD
Nancy, France
8 January 1990

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Association of Coronary Artery Disease in Cardiac Transplant Recipients with Cytomegalovirus Infection

We are concerned that the recent article by McDonald et al,[1] which concluded that cytomegalovirus (CMV) infection in heart transplant recipients is a risk factor for coronary occlusive disease, may have

been influenced by a failure to ameliorate episodes of CMV infection with a specific anti-CMV drug such as ganciclovir.[2] The analysis of rejection and infection factors using the log-rank test as separate K factors is not valid because they are both time-dependent covariates.[3] Nor is mention made of checking the proportional hazards assumption,[3] both of which may seriously flaw the authors' conclusions.

Our own policy is to treat all symptomatic donor-CMV seropositive/recipient-CMV seronegative mismatches with 14 days of intravenous ganciclovir when symptoms or signs develop. Of our 345 heart transplant recipients, 50% have an episode of rejection within a month of transplantation and 34 acute rejection deaths have occurred to date. In the previous Stanford article on this same topic,[4] between 84 and 91% of all patients had at least 1 rejection episode by the end of the first year. Nine episodes of rejection in 102 patients is, therefore, a remarkably low incidence, which we feel requires further explanation.

J.P. Scott
S.R. Large
P. Schofield
R.L. Smyth
E. Solis
N. Caine
J. Wallwork
Cambridgeshire, United Kingdom
12 December 1989

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REPLY: We appreciated the comments by Scott and colleagues.

The potential factors for the low incidence of acute graft rejection in our cardiac transplant recipients have been extensively discussed in previous papers from our group.[1,2] Striking differences exist among apparently similar immunosuppressive protocols in terms of dosage and timing of the drugs, which, in our opinion, may well explain the different incidences of rejection. At our center, on average, the maintenance doses of CSA, azathioprine and prednisone are higher than at Stanford University.

Our study was retrospective and was not designed to assess whether any antiviral therapy was effective or not in reducing the incidence of posttransplant coronary disease. In our patients, there was no appreciable difference in the mode of presentation of CMV infection between those who developed CAD and those who did not. Two patients in each group were treated with ganciclovir.

The use of prognostic variables that can change over time does present problems, especially if the length of follow-up differs between subgroups formed by potential prognostic variables. In our study, follow-up times were similar for the time-dependent variables. Only 1 of 9 acute rejec-

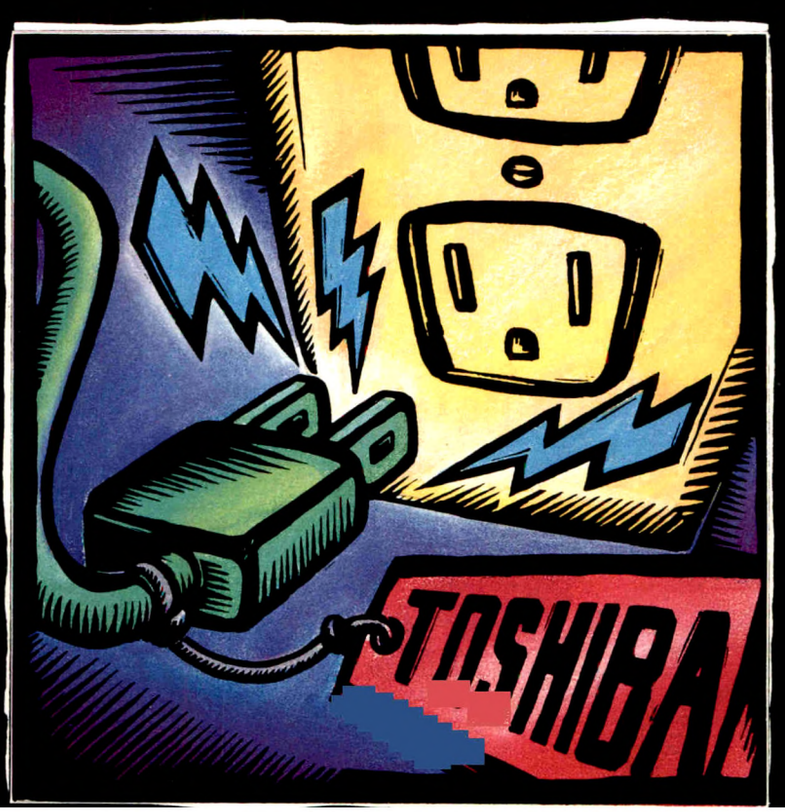
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A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy** – Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy** – Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions** – (A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility** – Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

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from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B** – Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers** – Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes** – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function** – Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children** – Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

References: 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-1245. 2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651. 3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J. B. et al. (eds.): *The Metabolic Basis of Inherited Disease,* 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642.

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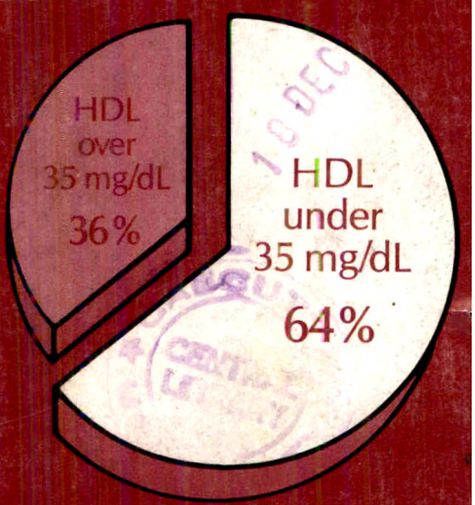
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*Defined as a combination of definite coronary death and/or definite myocardial infarction.

References: 1. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. *J Clin Invest.* 1973;52:1533-1543. **2.** Assmann G, Schulte H. *PROCAM-Trial: Prospective Cardiovascular Münster Trial.* Zürich: Panscientia Verlag; 1986:8-9. **3.** Data on file, Medical Affairs Dept, Parke-Davis.

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The American Journal of Cardiology

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OCTOBER 26, 1990

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GUEST EDITORS:

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Director, Cardiac Catheterization and Pacemaker Laboratories
Johns Hopkins Medical Institutions
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Gerald L. Wolf, MD, PhD
Visiting Professor of Radiology
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The American Journal of Cardiology

OCTOBER 26, 1990 VOL. 66 NO. 14

A SYMPOSIUM: Cardiovascular Imaging in the 1990s

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Director, Cardiac Catheterization and Pacemaker Laboratories
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Editor's suggestion: The symposium issues for a full year should be bound together separately from the regular issues.

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Introduction

Jeffrey A. Brinker MD

Imaging of the heart and great vessels has become the cornerstone of cardiac diagnoses and therapy. Whereas the hemodynamic and angiographic information provided by the traditional cardiac catheterization has played an essential role in our understanding of normal and abnormal cardiac physiology, newer, less invasive techniques have now supplanted this procedure in some situations and augmented it in others. There is the hope that continued technologic evolution will allow detailed evaluation of anatomy and physiology of the heart at reasonable expense and with minimal risk to the patient. This supplement of *The American Journal of Cardiology* reflects the proceedings of a symposium held in April of 1990, the purpose of which was to allow for an interchange of ideas as to where cardiac imaging is now and the directions that it might take in the future.

A major focus of discussion is angiography, which remains the only methodology capable of defining coronary anatomy with the degree of detail necessary for consideration of revascularization. In 1990, approximately 1.4 million cardiac angiographic procedures will be performed in the United States, almost all directed at assessing coronary artery anatomy. Relatively few of these patients will undergo coronary angiography because of uncertainty as to whether ischemic disease is present. Rather, angiography is applied to quantitate the extent of disease and to define candidacy for therapy (in particular, revascularization therapy). Fifteen years ago the pendulum of aggressiveness was taking a more conservative swing. Surgical revascularization had lost much of its luster, and non- and minimally invasive diagnostic techniques were threatening the preeminence of cardiac catheterization as the "gold standard" for cardiac assessment. Few would have predicted the tremendous growth in the number of angiographic procedures, and the concomitant proliferation of catheterization laboratories and invasive cardiologists that has since occurred. Then again, few could foresee the success of catheter-based interventional techniques in the treatment of cardiovascular disease.

Since the definition of candidacy, application, assessment of results, and, to a degree, risk of interventional procedures result from the direct installation of contrast media into the coronary arteries, it is fitting that a large portion of this symposium be directed at the catheterization laboratory and specifically at developments in contrast media that may significantly influence the patient's experience with angiography. From the questions and comments of those in attendance, the choice of radiographic contrast has become of increased concern to the practitioner. Whereas the development of better tolerated and "safer" contrast material has the potential to reduce the incidence of complications of angiography, few of us can ignore their impact on catheterization laboratory economics. We also note that other cardiac imaging modalities are improving rapidly. Magnetic resonance equipment can obtain spectacular images, chemical spectra and even chemical spectra displayed in an imaging format. Contrast agents for magnetic resonance are proliferating and appear to have relevant indicator properties. Cardiac metabolism can be studied with positron emission tomography, a technique capable of supplying unique insight into ischemic states.

Thus, for cardiac imagers, there appears to be an embarrassment of riches. It is hoped that the information that follows will provide some insight into the contrast controversy as well as a glimpse of methodologies that may someday replace angiography as a diagnostic tool.

Contrast Media: The Relation of Chemical Structure, Animal Toxicity and Adverse Clinical Effects

Torsten Almén, MD

Chemotoxicity and osmotoxicity of contrast media (CM) are determined by chemical structure. The lower the chemotoxicity and osmotoxicity of the CM, the less animal toxicity and higher clinical tolerance in humans will be achieved. Nonionic monomers such as iohexol and iopamidol in iodine-equivalent concentrations have approximately half the osmolality and therefore half the osmotoxicity of ionic monomers such as diatrizoate, iodamide, iothalamate and metrizoate. Absence of carboxyl groups in nonionic CM, as opposed to the presence of carboxyl groups in ionic CM, results in a lower chemotoxicity in nonionic CM. Similarly, a larger number of hydroxyl groups in nonionic CM than in ionic CM result in a lower chemotoxicity. The lower chemotoxicity of nonionic CM is reflected as a higher subarachnoid and intravenous tolerance both in animals and in the clinical setting.

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Four types of contrast media (CM) are currently used in diagnostic radiology for urography, angiography and computed tomography: ionic monomers (Fig. 1); ionic monoacidic dimers (Fig. 2); nonionic monomers (Fig. 3); and nonionic dimers (Fig. 4).

CHEMICAL PROPERTIES OF CONTRAST MEDIA

Important differences in chemical structures among these 4 types of CM are: the presence of a carboxyl group in ionic CM (Figs. 1 and 2) and the absence of a carboxyl group in nonionic CM (Figs. 3 and 4); the presence of 1 iodinated benzene ring in monomers (Figs. 1 and 3) and the presence of 2 iodinated benzene rings in dimers (Figs. 2 and 4). Currently available nonionic monomers have at least 4 hydroxyl groups/molecule to achieve a high water solubility (Fig. 3), while the ionic CM have no hydroxyl except for ioxithalamate and ioxaglate, with 1 hydroxyl group/molecule (Figs. 1 and 2). Ionic CM do not need hydroxyl groups to achieve water solubility, because their carboxyl group strongly contributes to their water solubility. Experience of the last two decades shows that the presence of several hydroxyl groups in a CM molecule may contribute both to a high water solubility and also to a low intravenous and subarachnoid toxicity.

It is logical that major differences in the chemical structures of different CM would result in important differences in animal toxicity, and the evolution of CM during the period 1920 to 1970 was characterized by a conscious search for chemical structures with increased tolerability in animals, often evaluated as the lethal dose for 50% of injected animals (LD_{50}). Increased animal tolerability of CM is paralleled by increased human clinical tolerability.

The same evolution continues, and the group of currently available CM (Figs. 1 to 6) with the highest animal tolerability is also the group that incurs the lowest frequency of all types of adverse reactions in the clinical setting. In animals, the nonionic monomers have a much lower subarachnoid neurotoxicity than the ionic monomers and dimers. The subarachnoid toxicity (or subarachnoid tolerability) has been evaluated as LD_{50} after intracerebral or intracisternal injections in mice and rats.[1,2] While subarachnoid LD_{50} for iohexol, iopamidol and metrizamide (nonionic monomers) was of a magnitude of 1,000 to 2,000 mg iodine/kg animal, the LD_{50} for ioxaglate, diatrizoate, iothalamate and metrizoate (ionic dimer and monomers) was below 200 mg iodine/kg animal. Thus, the subarachnoid tolerability in animals was about 10 times higher for the best nonionic monomers than for the ionic monomers and the ionic monoacidic dimer.

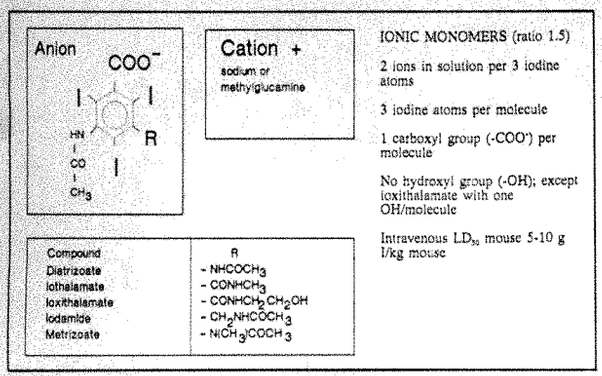


FIGURE 1. Ionic monomers (ratio 1.5). Examples are diatrizoate, iothalamate, ioxithalamate, iodamide and metrizoate. LD_{50} = lethal dose for 50% of injected animals.

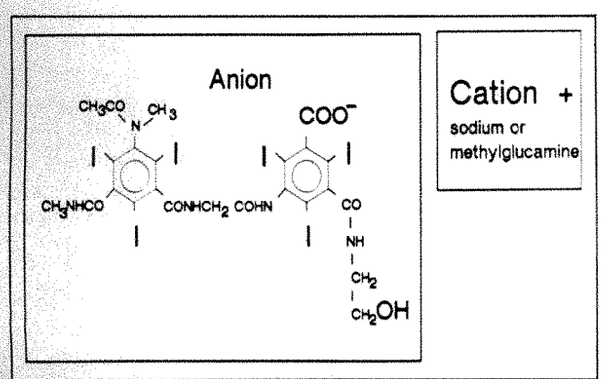


FIGURE 2. Ionic monoacidic dimers (ratio 3), ioxaglate. LD_{50} = lethal dose for 50% of injected animals.

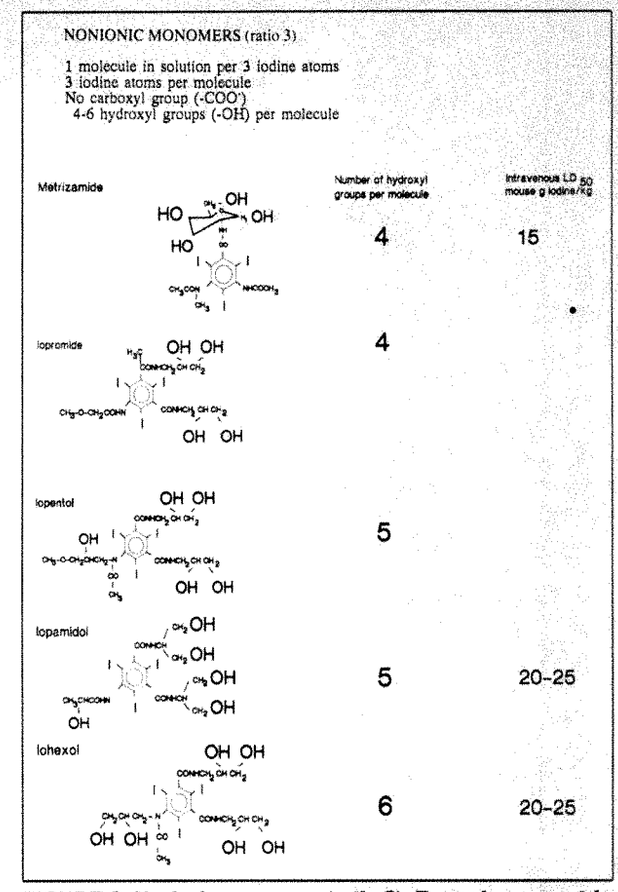


FIGURE 3. Nonionic monomers (ratio 3). Examples are metrizamide, iopromide, iopentol, iopamidol and iohexol. LD_{50} = lethal dose for 50% of injected animals.

In clinical myelography, the nonionic monomers produced such a low frequency of adverse reactions compared to the ionic CM that the latter were abandoned for that type of procedure. In particular, when nonionic CM replaced ionic CM, the incidence of seizures and other signs of excitation was much lower.[3-9]

In animals, the nonionic monomers have about a 3 times higher intravenous tolerability than the ionic monomers, evaluated as LD_{50} (Figs. 1, 3, and 5). While the intravenous LD_{50} in mice for ionic monomers (diatrizoate, iothalamate, metrizoate) is in the magnitude of 5 to 10 g iodine/kg animal, the intravenous LD_{50} for nonionic monomers (metrizamide, iohexol and iopamidol) is in the magnitude of 15 to 25 g iodine/kg animal.[2,10,11]

In clinical intravascular use, the lower frequency of adverse reactions associated with the nonionic monomers[12-17] has led to their increasing use. In arteriography, the nonionic monomers produce much less pain compared to ionic monomers. In arterial or venous injection, the frequency of gastrointestinal reactions, such as nausea or vomiting, was 4 to 5 times lower and the frequency of such skin reactions as urticaria, itching and exanthema was 6 to 7 times lower with a nonionic monomer than with an ionic monomer.[15]

Subsequent studies of 50,000[16] and 300,000[17] patients, respectively, confirmed the lowered incidence of adverse effects with nonionic versus ionic monomers.

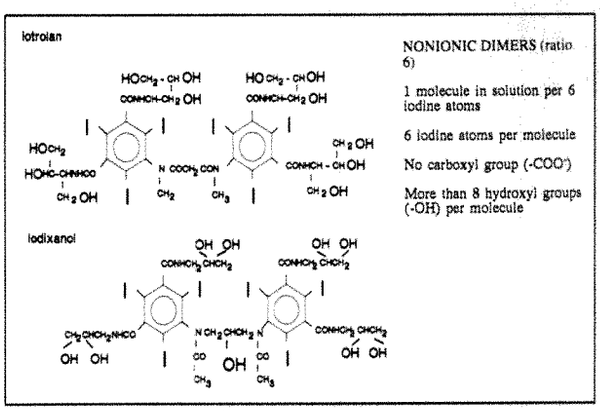


FIGURE 4. Nonionic dimers (ratio 6). Examples are iotrolan and iodixanol.

PRIMARY AND SECONDARY EFFECTS OF CONTRAST MEDIA

The primary effect of CM is the attenuation or absorption of radiation on its way from a roentgen tube to a roentgen film. All other CM effects may be regarded as adverse, and they may or may not be observed clinically.

All currently available water-soluble CM used in diagnostic radiology contain iodine atoms for attenuation

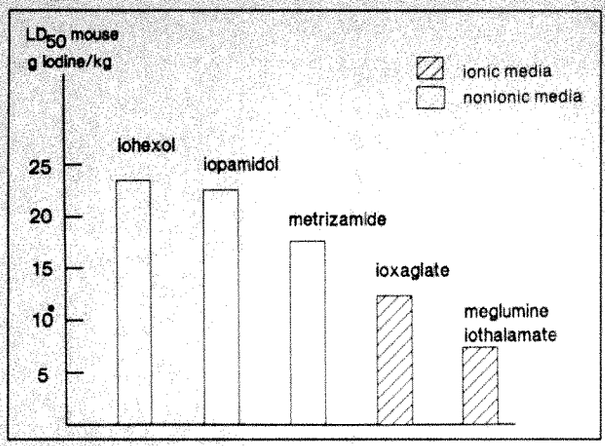


FIGURE 5. Acute intravenous LD_{50} of CM in mice.[1,2] LD_{50} = lethal dose for 50% of injected animals.

of radiation. Iodine was introduced in CM about 60 years ago, and since then there has been no improvement in the primary effect of CM.

The secondary or toxic effects of CM are the sum of chemotoxicity, osmotoxicity and ion toxicity. Chemotoxicity of a CM molecule can be due to binding of proteins, effect on cell membrane or organelles, blocking of enzymes and release of vasoactive substances from cells. Osmotoxicity or osmotic effect of a CM solution is due to its ability to induce water movements across membranes of the body. Among osmotic effects are pain in arteriography, vasodilatation with hypotension and rigidification of red blood cells. Ion toxicity can be due to too high or too low a concentration of various ions that interferes with cellular function.

PROPERTIES OF AVAILABLE CONTRAST MEDIA

Figure 1 shows the chemical structures of commonly used ionic monomers, so called because they contain 1 unit or mer of a benzene ring with 3 iodine atoms that attenuate radiation. They are called ionic because they contain 2 ions. There is 1 negatively-charged anion, which is the diatrizoate, iodadamide, iothalamate or metrizoate ion, each containing 3 iodine atoms and 1 carboxyl group. They contain 1 positively-charged cation, which is often a sodium or a methylglucosamine (meglumine) ion.

Interest in the osmotoxicity of CM has led to the concept of a ratio between the "imaging effect of the CM" (the number of iodine atoms) and "osmotic effect of the CM" (the number of particles in an ideal solution). The numerical value of this ratio is the number of iodine atoms divided by the number of particles.

For ionic monomers, the division of 3 iodine atoms by 2 particles results in the numerical value of 1.5; hence, ionic monomeric CM are also called ratio 1.5 CM.

The higher the ratio, the lower the osmotoxicity of CM. The ratio 3 CM have twice as many iodine atoms per particle as the ratio 1.5 CM. This means that at equal imaging effect the ratio 3 CM have half the osmotic effect (osmotoxicity), as the ratio 1.5 CM. Similarly, the ratio 6 CM have twice as many iodine atoms per particle in solution as the ratio 3 CM, and therefore half the osmotoxicity (Figs. 1 to 4).

Figure 1 shows that the only difference between the individual ionic monomeric ratio 1.5 CM is a side chain marked "R" that determines whether the CM is diatrizoate, iothalamate, ioxithalamate, iodamide or metrizoate. All ionic monomeric CM contain 1 carboxyl group/molecule, which is responsible in large part for the high neurotoxicity of these CM that renders them unsuitable for myelography.

The small differences in chemical structure among the ionic monomeric CM result in an approximately equal chemotoxicity and also a roughly equal osmotoxicity. Ionic monomers, all of which are ratio 1.5, are referred to as "high osmolar CM," while the ratio 3 and 6 CM are called "low osmolar CM." The latter term includes CM with great differences in chemical structure and toxicity (i.e., nonionic monomers and dimers and ionic monoacidic dimer).

In summary, ionic monomers have the lowest viscosity, the highest osmotoxicity (ratio 1.5 CM), the lowest intravenous tolerance in animals (intravenous LD_{50}, 5 to 10 g iodine/kg) and the lowest subarachnoid tolerance in

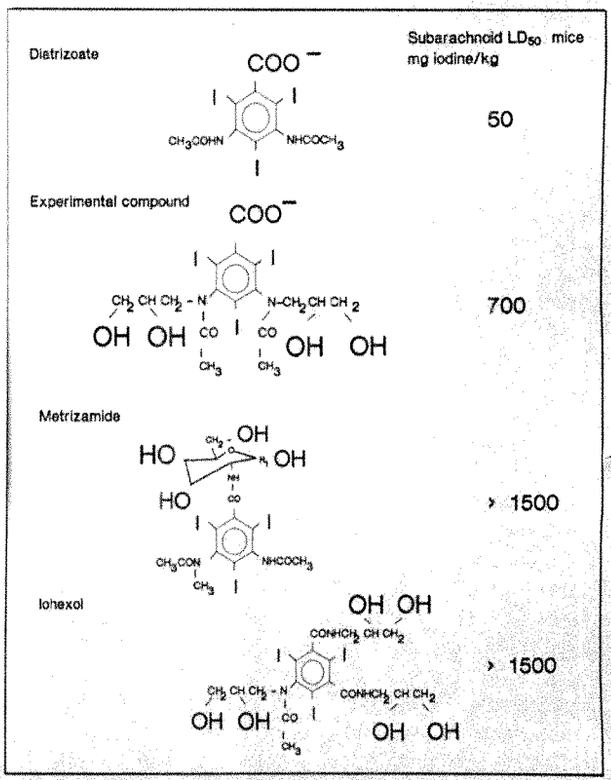


FIGURE 6. Different types of CM and their subarachnoid LD_{50} in mice,[1,2] (and unpublished observations by H. Drobeck and S. Salvesen). LD_{50} = lethal dose in 50% of injected animals.

animals (subarachnoid LD_{50}, <200 mg iodine/kg) (Figs. 1, 5 and 6).

Iopamidol and iohexol, 2 of the second generation of nonionic monomers (Fig. 3) with more than 4 hydroxyl groups or other hydrophilic groups, have been in clinical use for some years and a number of new CM in this group are now in early clinical or preclinical trials. These CM have an intermediate viscosity, intermediate osmotoxicity (ratio 3 CM), the highest intravenous tolerance in animals (intravenous LD_{50}, 20 to 25 g iodine/kg) and highest subarachnoid tolerance in animals (subarachnoid LD_{50}, >1,500 mg iodine/kg) (Figs. 3, 5, and 6).

An ionic ratio 3 CM has been synthesized (Fig. 2). It is an ionic monoacidic dimer, ioxaglate, with 6 iodine atoms for each pair of ions (1 cation without iodine, and 1 anion with the 6 iodine atoms). It has 1 carboxyl group and therefore should not be used for myelography. It contains 1 hydroxyl group. Ioxaglate has an intermediate viscosity, intermediate osmotoxicity (ratio 3 CM), intermediate intravenous tolerance in animals (intravenous LD_{50}, 10 to 15 g iodine/kg) and the lowest subarachnoid tolerance in animals (subarachnoid LD_{50}, 200 mg iodine/kg) (Figs. 2, 5, and 6).

The first nonionic dimers, iotrolan and iodixanol, are under development (Fig. 4). These ratio 6 CM have 6 iodine atoms/molecule and 9 or more hydroxyl groups/molecule. Like the nonionic monomers, they form molecular solutions and do not dissociate. Nonionic dimers have the lowest osmotoxicity of the water-soluble CM. On the other hand, they have the highest viscosity because they are the largest CM molecules with the highest number of hydroxyl groups. The high viscosity, in combination with the low osmolality, means the highest urine viscosity. Thus, the nonionic dimers have the advantage of lower osmolality (i.e., osmotoxicity) than nonionic monomers but the disadvantage of higher viscosity of CM solutions and CM urine. Nonionic dimers have the highest intravenous tolerance and highest subarachnoid tolerance in animals. Future studies will determine the clinical role of these nonionic dimers.

DEVELOPMENT OF NONIONIC LOW-OSMOLALITY CONTRAST MEDIA

Development of the first nonionic monomer, metrizamide, was spurred by the desire to decrease CM-induced pain in arteriography attributed to the high osmololality of the commonly used ionic monomeric CM.[18,19] The high clinical tolerability of metrizamide led to the synthesis of other new nonionic monomers, such as iopamidol, and iohexol, and the synthesis of other low osmolar CM, such as the ionic monoacidic dimeric ioxaglate, and the nonionic dimeric CM, iotrolan (Figs. 1 to 4).

In the 1960s, I theorized that transforming an ionic monomer to a nonionic monomer (Figs. 7 and 8) would reduce osmolality, and thus the pain associated with arteriography. This transformation is accomplished by 3 major changes in chemical structure: elimination of the carboxyl group; simultaneous elimination of the positive ion; and achieving water solubility by binding a number of hydrophilic hydroxyl groups (Fig. 8) at different sites around the molecule.

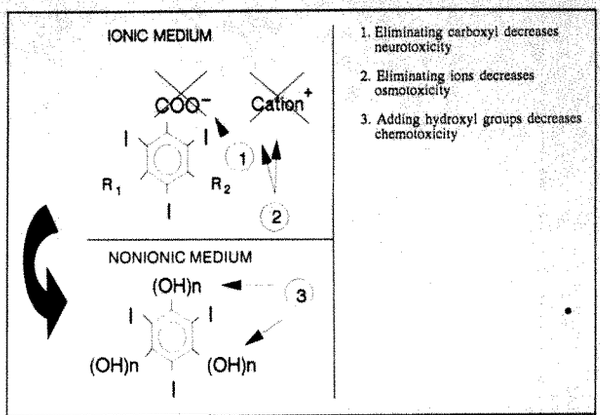


FIGURE 7. Transformation of an ionic monomer to a nonionic monomer involves elimination of carboxyl groups and ions from the ionic monomer and addition of hydroxyl groups to the nonionic monomer.

These ideas came to fruition in 1968, when the synthesis of water-soluble, nonionic CM was initiated. The chemical structures presented in Figure 8 were eventually incorporated in iohexol and other nonionic CM.

The elimination of the carboxyl group gave metrizamide (Fig. 6) its low subarachnoid neurotoxicity. It was noted that metrizamide had an osmolality (osmotoxicity) about half that of the ionic monomer metrizoate, but it had subarachnoid toxicity in animals at least 10 times lower than metrizoate. Thus, it became evident that reduced osmotoxicity was not the only reason for the high subarachnoid tolerability of nonionic monomers in animals and humans; a reduced chemotoxicity due to the absence of carboxyl groups was found to be the most important part of the explanation (Fig. 6).

Metrizamide was the first water-soluble CM with such a low subarachnoid toxicity that it came to be used around the world for myelography. In 1977, a study of metrizamide in arteriography was the first report[20] that a nonionic monomer produced far less pain in arteriography than an ionic monomeric ratio 1.5 CM.

The mechanisms responsible for CM-induced pain and the difference in pain thresholds among different vascular regions are unknown. Currently, the degree of pain produced by CM in arteriography is believed to be related to their degree of hypertonicity versus normal serum.

The next nonionic monomeric CM to be synthesized were iopamidol and iohexol. Figures 3 and 6 show that the hydroxyl-carrying side-chains are evenly distributed all around the CM molecule, and these CM have an even lower intravenous and subarachnoid toxicity than metrizamide. This led to the hypothesis that "nonionic CM get a lower subarachnoid and intravenous toxicity when the hydroxyl groups or other hydrophilic groups are evenly distributed around the molecule than when concentrated at 1 end of the molecule."

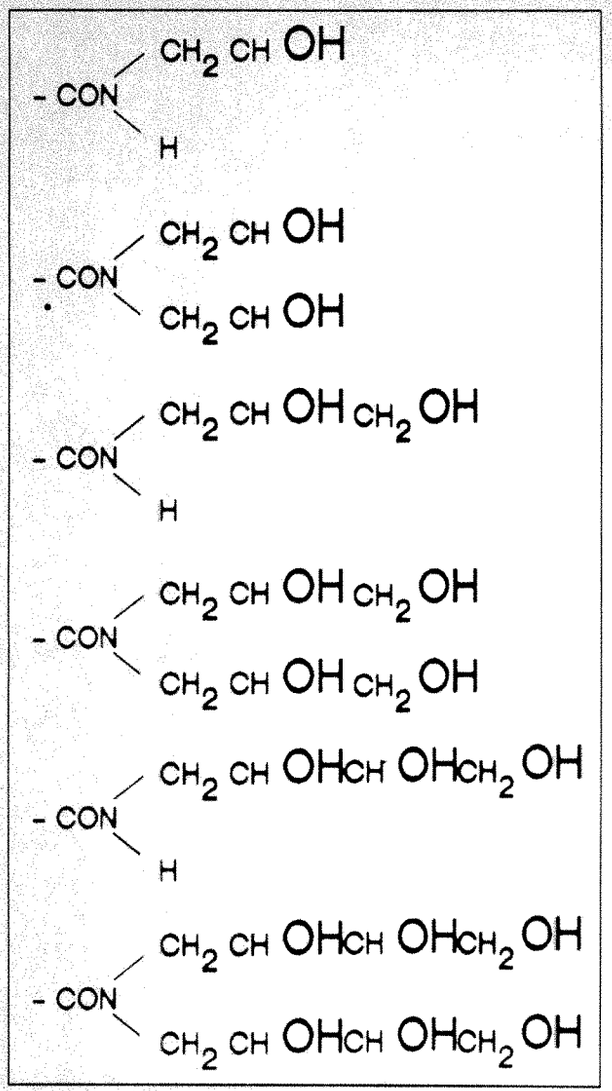


FIGURE 8. Some hydrophilic structures suggested for covalent bonding to a benzene ring with 3 iodine atoms to obtain a nondissociating (nonionic) water soluble contrast media molecule.

GUIDELINES FOR PREDICTING ANIMAL TOXICITY AND CLINICAL TOLERANCE OF CONTRAST MEDIA ACCORDING TO CHEMICAL STRUCTURE

Four simple rules serve as guidelines to help predict the biologic properties of a water-soluble iodinated CM with a known chemical structure. In the tradition of scientific inquiry, if results of future experiments fit these rules, then they are confirmed. If not, then new rules have to be formulated and then tested.

Rule I states that "use of CM with a ratio 3 or higher almost completely eliminates arteriography pain." According to this rule, we predict that ionic monomers (diatrizoate, iothalamate and metrizoate) will often produce pain in arteriography because their ratio is lower than 3. Similarly, we predict that the ionic dimer (ioxaglate) and the nonionic monomers (iohexol, iopamidol and others), which are all ratio 3, should produce less arteriography pain than the ratio 1.5 CM. These predictions dovetail with our clinical experience.[21-24]

We predict that the ratio 6 CM will produce the least discomfort in arteriography among the previously developed water soluble CM. Future studies will determine whether this prediction is correct.

Rule II states: "The lower the number of particles in solution (higher ratio), the lower the number of carboxyl groups, and the higher the number of hydroxyl groups in relation to the number of iodine atoms in a CM molecule, the higher its intravenous tolerance will be."

Ionic monomeric CM have all the properties predicting a high animal toxicity (low tolerance) (Fig. 1), and rule II predicts that this group of CM will have the lowest intravenous tolerability. Animal studies (Fig. 5) show this prediction to be correct, and the ionic monomers do have the lowest intravenous tolerance (5 to 10 g iodine/kg) among the different types of CM.

The ionic monoacidic dimer (ioxaglate) contains 1 carboxyl group and 1 hydroxyl group, 2 ions, and 6 iodine atoms/molecule (Fig. 2) and it is a ratio 3 CM. Rule II predicts the intravenous tolerance of the ionic dimer to be higher than that of the ionic monomers. Animal studies (Fig. 5) show ioxaglate to have an intravenous tolerance of 10 to 15 g iodine/kg, higher than that of the ionic monomers.

The nonionic monomer metrizamide has no carboxyl group (Fig. 3), and has 4 hydroxyl groups situated at 1 end of the molecule. It is a ratio 3 CM. Rule II predicts the intravenous tolerance of the ratio 3 CM metrizamide to be higher than that of the ratio 3 CM ioxaglate. Animal investigations (Fig. 5) confirm this prediction.

The new ratio 3 nonionic monomers, iohexol and iopamidol, have no carboxyl group and many hydroxyl groups evenly distributed around the molecule (Fig. 3). Rule II predicts that these will have higher intravenous tolerance than metrizamide, due to the higher number of hydroxyl groups, and animal studies confirm this. These results have led us to develop the rule that "even distribution of hydroxyl groups around the CM molecule gives lower intravenous toxicity than distribution of all hydroxyl groups at 1 end of the molecule."

Rule III stipulates that "a low neurotoxicity in the subarachnoid space requires absence of carboxyl groups and many hydroxyl groups evenly distributed around the CM molecule." Figure 6 shows the diatrizoate molecule with 1 carboxyl group and no hydroxyl group, and an experimental compound with 1 carboxyl group and 4 hydroxyl groups. Subarachnoid tolerance is higher for the experimental compound than for diatrizoate, demonstrating that introduction of hydroxyl groups decreases the subarachnoid neurotoxicity of CM.

The experimental CM and metrizamide (Fig. 6) both have 4 hydroxyl groups, but only metrizamide does not contain a carboxyl group. The subarachnoid tolerance of metrizamide is higher than that of the experimental compound. Thus, eliminating the carboxyl group markedly

reduced CM neurotoxicity. Therefore, CM-containing carboxyl groups should not be used for myelography or for enhancement in computed tomography in cases when a damaged blood-brain barrier is suspected, because this would allow contact between nerve cells and intravascularly injected carboxyl-containing CM.

Figure 6 shows metrizamide with 4 hydroxyl groups at 1 end of the molecule compared with iohexol with 6 hydroxyl groups evenly distributed around the molecule. When animals are premedicated with chlorpromazine, at a given dose of CM all get seizures after subarachnoid injections of metrizamide, but none do after iohexol.[25] This supports the assumption that symmetrical distribution of hydroxyl groups around the CM molecule decreases its subarachnoid neurotoxicity.

Figure 9 shows the injection of CM molecules (black dots) into an artery. In the capillaries, CM diffuses out of the vessels, and the smaller the CM molecule, the faster the diffusion. At the venous end of the capillaries, water is drawn into the vessels, and the higher the osmolality of the CM solution, the more water is drawn into the vessels. These mechanisms make the CM concentration in the draining vein lower than in the injected artery. To obtain an optimal venous phase in arteriography with a high venous CM concentration, follow rule IV.

Rule IV states that a high venous concentration is obtained when a diffusion of CM is slowed by using large molecules (dimers) and osmotic effects are decreased by using CM with low osmotic effects (ratio 3 or ratio 6). Ionic monomeric ratio CM (Fig. 1) are small and diffuse rapidly out of the vessels. They have a high osmolality and draw much water into the vessels. Therefore they get the lowest venous concentration among the 4 types of CM in Figures 1 to 4.

Nonionic monomers (Fig. 3) are small molecules that diffuse quickly out of the vessels. They have a lower osmolality (ratio 3), and they draw less water into the vessels than ratio 1.5 CM. Therefore, their venous concentrations become somewhat higher than those of ionic monomers.

The ionic monoacidic dimer (Fig. 2) is a larger molecule. It should diffuse more slowly out of the vessels than monomers. It has a low osmolality (ratio 3) and draws only little water into the vessels. Therefore its venous concentration becomes still higher than that of the nonionic monomers.

Nonionic dimers (Fig. 4) are large molecules that diffuse slowly, and they have an even lower osmolality than that of ionic dimers. Therefore, it is predicted that the nonionic dimers will get the highest venous concentration.

CONTRAST MEDIA TOXICITY IS THE SUM OF MANY SECONDARY EFFECTS

The adverse effects of CM are due to a combination of chemotoxic effects of the CM molecules, osmotoxic effects and effects of suboptimal ion concentrations in the CM solution. Among the possible secondary or adverse effects of CM are: vasodilatation with possible arterial hypotension; rigidification of red blood cells with possible pulmonary hypertension; vascular effects with pulmonary edema; effects on glomerular membrane with proteinuria and effects on renal vessels or tubular cells with anuria; cardiac effects with decreased contractile force and ventricular fibrillation; interaction with various enzymes; breakdown of the blood-brain barrier with direct CM effects on brain (seizures); damage of endothelial cells with thrombus formation and emboli from those thrombi or release of substances from endothelial cells causing an anaphylactoid reaction; direct cellular effects with release of histamine, serotonin, or other substances causing symptoms of anaphylactoid reaction; and interaction with antibodies with pure anaphylaxis (probably rare).

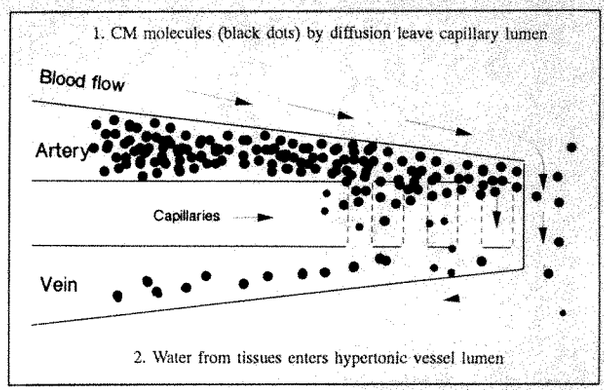


FIGURE 9. When contrast media (CM) molecules *(black dots)* are injected into an artery the CM molecules, by diffusion, leave the capillary lumen and water from tissues enters the hypertonic vessel lumen. This produces a lower CM concentration in the draining veins than in the injected artery.

GUIDELINES FOR DECREASING THE FREQUENCY OF CONTRAST MEDIA-ASSOCIATED ADVERSE EFFECTS

Choose a CM that is superior to other media with regard to both chemotoxicity and osmotoxicity. Thus, nonionic monomeric CM are preferable to ionic monomeric CM, because animal experiments and clinical experience have shown that 3 properties of nonionic monomeric CM (which are not properties of ionic monomers) are associated with reduced toxicity (Figs. 1 and 3): absence of carboxyl groups, resulting in a lower subarachnoid and intravenous toxicity for the nonionic monomers; a larger number of hydroxyl groups, giving nonionic CM a lower acute intravenous and subarachnoid toxicity than ionic CM; a higher ratio of 3 between number of iodine atoms and number of particles in solution, giving nonionic monomers a lower osmotoxicity than ionic monomeric CM (ratio 1.5).

Nonionic monomeric CM are also preferable to ionic monoacidic dimeric CM because animal experiments and clinical experience have shown 2 properties of the chemical structure of nonionic monomers, which the ionic monoacidic dimer does not contain, can be linked to reduced toxicity (Fig. 5): absence of carboxyl groups and a

larger number of hydroxyl groups, resulting in a lower acute intravenous and subarachnoid toxicity compared to that of an ionic monoacidic dimer.

Future clinical experience will determine optimal use of nonionic monomers and dimers. Nonionic dimers have the advantage of lower osmotoxicity, while nonionic monomers have the advantage of lower viscosity of CM solution and lower viscosity of CM urine. Clinical comparisons between these 2 types of media are currently in progress.

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Cardiovascular Effects of Iodinated Contrast Agents

John W. Hirshfeld, Jr., MD

The ideal intravascular contrast agent would be biologically inert and have no pharmacologic actions. Pharmacologic actions of currently used radiographic contrast agents are determined principally by 3 physicochemical properties of the iodine-bearing molecule and its formulation: osmolality, sodium concentration and calcium-binding properties. Within this framework, the calcium-binding 1.5 ratio agents have the most marked effects, and the 3.0 ratio nonionic agents the least, with the noncalcium-binding formulations of 1.5 ratio agents and ioxaglate (the only 3.0 ratio ionic agent) in between. Differences in hemodynamic effects are predominantly related to osmolality with the 3.0 agents causing less hemodynamic disturbance. The magnitude of difference is small enough that the 3.0 ratio agents have no important clinical advantage when used in patients with good or moderately impaired left ventricular function. However, the difference may be important in patients with severely impaired circulatory performance. The principal electrophysiologic differences are between the calcium-binding 1.5 ratio agents (which are associated with a clear-cut greater frequency of ventricular fibrillation during coronary injection than the noncalcium-binding 1.5 ratio agents) and the 3.0 ratio agents.

There is no justification for the use of calcium-binding 1.5 ratio agents, since noncalcium-binding formulations of the same molecule are available at the same price. The circulatory reserve of most patients makes the differences between 3.0 ratio agents and noncalcium-binding 1.5 ratio agents clinically unimportant. In view of the substantial price disparity between 1.5 ratio and 3.0 ratio agents, noncalcium-binding 1.5 ratio agents are appropriate for patients with good circulatory performance and 3.0 ratio agents are best reserved for patients with impaired circulatory performance. The definition of the appropriate boundary between those patient groups requires further research.

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Currently there are 8 commercially available iodinated contrast agent products used for cardiac angiography in the United States. On the basis of their chemical and pharmacologic properties, they may be classified into 2 large groups: high- and low-osmolar agents. Each group may then be further divided into 2 subgroups. Low-osmolar agents may be classified as either nonionic or ionic subgroups. High-osmolar agents (which are all ionic) may be divided into calcium-binding and noncalcium-binding subgroups.

The iodine ratio forms the fundamental basis for classifying a contrast agent molecule (i.e., the ratio of the number of iodine atoms in the molecule to the number of osmotically active particles that the molecule produces in solution). This property is the basis of the first grouping: 1.5 ratio agents (classified as high-osmolar ionic agents) and 3.0 ratio agents (classified as low-osmolar agents). There are global differences in properties between the 1.5 ratio and the 3.0 ratio groups. In addition, within each group the 2 subgroups have distinguishable chemical and pharmacologic properties.

Most of the currently available 1.5 ratio agents use diatrizoic acid as the iodine-bearing molecule. Since this molecule, which contains 3 iodine atoms, achieves water solubility by ionization of the carboxyl group at the 1 position, it produces 2 osmotically active particles in solution. Commercially available formulations of diatrizoic acid may be further subdivided on the basis of calcium-binding properties (Table I). Two of the available formulations (MD 76™, Renografin 76™) contain sodium citrate and noncalcium-enriched ethylene-diamine-tetraacetic acid (EDTA), which confer calcium-binding activity to the formulations. The other 2 (Angiovist™, Hypaque 76™) contain no citrate and the EDTA in their formulations is calcium enriched. Hence, they do not bind calcium to the same degree.

Currently, there are 4 different 3.0 ratio molecules available in the U.S., subgrouped on the basis of 2 different strategies used to achieve their iodine ratio. Ioxaglate is a molecule that contains 6 iodine atoms and achieves water solubility by ionization; thus, it is a 3.0 ratio ionic agent. Iohexol, iopamidol and ioversol (each of which have 3 iodine atoms/molecule) achieve water solubility by having nonionizing but hydrophilic moieties in the 1, 3, and 5 positions; thus, they are 3.0 ratio nonionic agents. All of the 3.0 ratio agents have noncalcium-binding formulations (Table I).

IMPORTANCE OF OSMOTIC EFFECTS OF CONTRAST AGENT FORMULATION

Many of the overall pharmacologic effects of contrast agents are a consequence of the osmolality of the formu-

TABLE I Comparison of the Chemical Compositions and Selected Physical and Pharmacologic Properties of Radiographic Contrast Agents Currently Used in Cardiac Angiography

	Angiovist	Hypaque-76	Renografin-76	MD-76	Vascoray
Iodine (mg/ml)	370	370	370	370	400
Iodine-containing molecule	Diatrizoate	Diatrizoate	Diatrizoate	Diatrizoate	Iothalamate
Cations	Meglumine Na	Meglumine Na	Meglumine Na	Meglumine Na	Meglumine Na
Intravenous LD_{50} (g iodine/kg)	7.5	7.5	7.5	7.5	6.2
Measured osmolality (mOsm/kg)	2,076	2,016	1,940	2,140	2,400
Viscosity (37°C)	8.4	8.32	8.4	9.1	9.0
Sodium concentration (mEq/liter)	160	160	190	190	408
Other additives	0.01%NaCaEDTA	0.01%NaCaEDTA	0.32%NaCitrate 0.04%NaEDTA	0.32%NaCitrate 0.04%NaEDTA	0.0125%NaH_2PO_4 0.011%NaCaEDTA
	Isovue	**Omnipaque**	**Optiray**	**Hexabrix**	
Iodine (mg/ml)	370	350	320	320	
Iodine-containing molecule	Iopamidol	Iohexol	Ioversol	Ioxaglate	
Cations	None	None	None	Meglumine Na	
Intravenous LD_{50} (g iodine/kg)	21.8	24.2	17.0	11.2	
Measured Osmolality (mOsm/kg)	796	844	702	600	
Viscosity (37°C)	9.4	10.4	5.8	7.5	
Sodium concentration (mEq/mL)	Trace	Trace	Trace	150	
Other additives	0.05%Na_2CaEDTA Tromethamine	0.01%Na_2CaEDTA Tromethamine	0.02%Na_2CaEDTA Tromethamine	0.01%Na_2CaEDTA	

EDTA = ethylenediaminefetraacetic acid; LD_{50} = median lethal dose.

lation. Because all agents must achieve an iodine concentration of at least 30% to provide adequate radiopacity for cardiac angiography,[1] osmolalities greater than that of blood plasma are required. At any particular iodine concentration, a 1.5 ratio agent will produce a solution osmolality roughly twice that produced by a 3.0 ratio agent.

Differences between the pharmacologic properties of contrast agent molecules are less marked if their properties are normalized to dose in terms of osmoles delivered rather than in terms of iodine delivered. An example of this difference is the mouse acute intravenous lethal dose in 50% of injected animals (LD_{50}) of the different agents (Table I). In these experiments, the test dose of contrast agent is typically administered intravenously over 1 to 2 minutes. The mode of death is acute pulmonary edema caused principally by acute expansion of intravascular volume. Differences in LD_{50} are roughly equivalent to differences in osmolality.

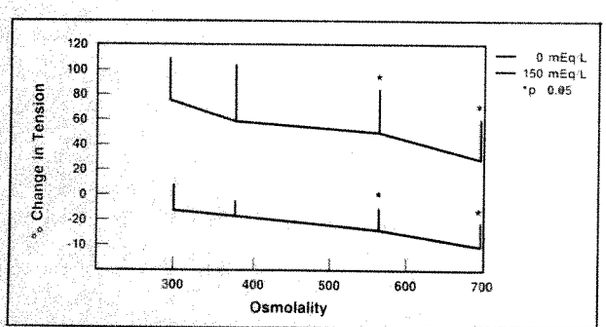


FIGURE 1. Graph of the percentage of change in developed tension as a function of osmolality for solutions with sodium concentration of 0 mEq/liter *(solid line)* and 150 mEq/liter *(dashed line)*. Solution osmolality was varied by varying the glucose concentration. Note that myocardial contractile force is increased by the sodium-free solutions and decreased by increasing solution osmolality. (Reproduced with permission from *Am Heart J.*[6])

IMPORTANCE OF THE OTHER CONSTITUENTS OF THE CONTRAST AGENT FORMULATION

Other substances in the contrast agent solution in addition to the iodine-bearing molecule (Table I) can have considerable influence on the overall pharmacologic properties of the formulation.

Sodium concentration: The formulations of all nonionic agents contain negligible quantities of sodium. On the other hand, the formulations of all ionic agents (both 1.5 ratio and 3.0 ratio) contain concentrations of sodium similar to that of blood plasma. The absence of sodium in the formulations of the nonionic agents contributes importantly to their pharmacologic properties.

Calcium binding: The formulations of all of the 3.0 ratio agents (ionic and nonionic) are noncalcium-binding. Thus, this property is not responsible for differences between the 3.0 ratio agents. On the other hand, the differences between calcium-binding and noncalcium-binding formulations of diatrizoic acid are substantial and greatly influence the pharmacologic properties of the individual formulations.

Because the calcium-binding properties of the formulations of the 1.5 ratio agents have such a great impact on their pharmacologic properties, and because the formulations of the 3.0 ratio agents are all noncalcium-binding, comparisons between the properties of calcium-binding 1.5 ratio agents and 3.0 ratio agents are invalid. Although such comparisons are potentially misleading, numerous

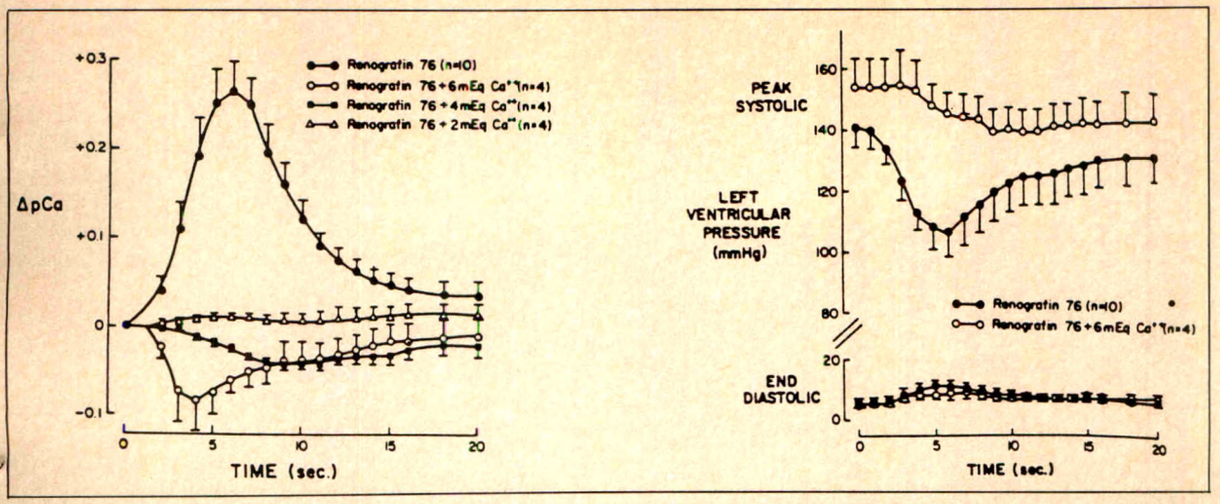


FIGURE 2. Effect of intracoronary injection of Renografin 76 (a calcium [Ca^{++}]-binding formulation of a 1.5 ratio agent) without and with various quantities of added calcium chloride on the time-related change in coronary venous pCa (− log of concentration of Ca^{++}) *(left)* and left ventricular peak systolic and end diastolic pressure *(right)*. Note that the addition of calcium chloride abolishes the decrease in coronary venous calcium ion concentration and attenuates the decrease in left ventricular peak systolic pressure in response to the injection. (Reproduced with permission from *J Am Coll Cardiol.*[14])

studies have been conducted in which a calcium-binding 1.5 ratio agent has been compared to a 3.0 ratio agent. When interpreting such studies, it is important to distinguish between the effects of the contrast agent molecule and the effects of its formulation.

PRIMARY EFFECTS OF CONTRAST AGENTS ON MYOCARDIAL CONTRACTILE PERFORMANCE

The overall effect of contrast agents on myocardial contractile performance results from 3 physicochemical properties of the contrast agent solution: osmolality, sodium concentration and calcium binding. Increasing solution osmolality above the osmolality of plasma decreases myocardial contractile force in a concentration-dependent manner (Fig. 1).[8] This phenomenon appears to be simply an effect of osmolality, which is applicable to solutions of any nontoxic molecule. Solutions with sodium concentrations below that of plasma have positive inotropic properties, presumably as a result of sodium-calcium exchange across the myocardial cell membrane.[9,10] Solutions that are hypertonic with respect to sodium have negative inotropic properties.[8,11] Solutions that have calcium-binding properties also have negative inotropic activity, presumably caused by extraction of intracellular calcium.[12,13] This phenomenon is illustrated by the different effects of intracoronary injection of Renografin 76 either with or without calcium enrichment (Fig. 2).[14]

Selective intracoronary injection of 1.5 ratio ionic agents in formulations containing clinically useful iodine concentrations depresses myocardial contractile force.[2–6] The magnitude of depression of contractile force caused by calcium-binding formulations is considerably greater than that caused by noncalcium-binding formulations.[7] On the other hand, selective intracoronary injection of 3.0 ratio nonionic agents causes a transient increase in myocardial contractile force (Fig. 3).[3] The effect of ioxaglate on myocardial contractile force is intermediate between 1.5 ratio agents and 3.0 ratio nonionic agents.

The overall effect of maximizing the differences of all 3 properties is illustrated in Figure 4, which compares the hemodynamic and coronary sinus ionized calcium response to the injection of Renografin 76 (a high-osmolar, sodium-containing, calcium-binding formulation) to the

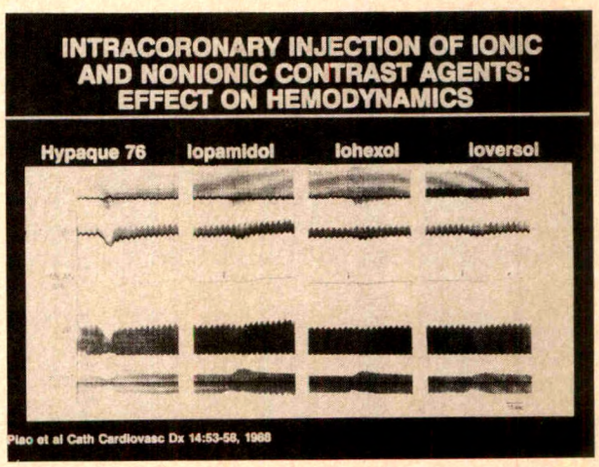


FIGURE 3. Recordings of hemodynamic parameters from an open-chest dog preparation showing the change in left ventricular pressure and dP/dt after the intracoronary injection of Hypaque 76 (H 76), a noncalcium-binding 1.5 ratio ionic agent, and three 3.0 ratio nonionic agents, iopamidol (IOP), iohexol (IOH) and ioversol (IOV). Note that while the ionic agent transiently depresses contractile force the nonionic agents cause a transient increase. ABP = aortic blood pressure; dP/dT = a measure of left ventricular contractile state; LVP = left ventricular pressure. (Reproduced with permission from Wiley-Liss, A Div. of John Wiley & Sons, Inc.[3])

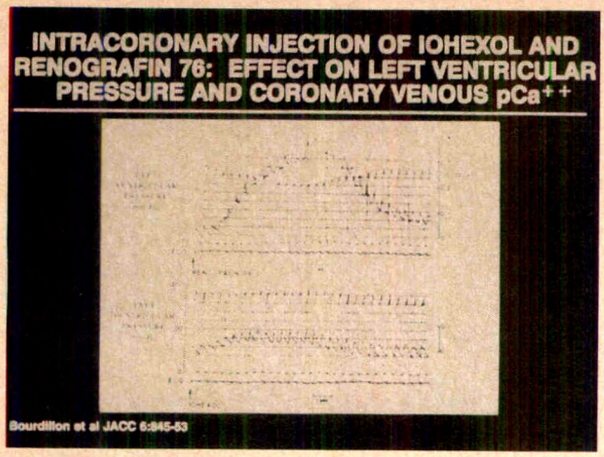


FIGURE 4. Experimental recordings of left ventricular pressure, electrocardiogram (ECG) and coronary venous pCa with single intracoronary injections of Renografin 76 *(top)* and iohexol *(bottom)*. Note that iohexol causes less of a decrease in coronary venous calcium ion concentration and does not cause a decrease in left ventricular peak systolic pressure. pCa = (− log of concentration of calcium^{++}). (Reproduced with permission from *J Am Coll Cardiol.*[14])

injection of a comparable volume of iohexol (a low-osmolar, sodium-free, noncalcium-binding formulation) (Fig. 4). Thus, from the point of view of myocardial contractile force, the ideal contrast agent formulation has a low osmolality, is sodium-free and is noncalcium-binding.

PRIMARY EFFECTS ON MYOCARDIAL OXIDATIVE METABOLISM

Bolus injection of contrast agents in volumes used for ventriculography causes changes in the pattern of myocardial oxidative metabolism that outlast the acute hemodynamic and electrophysiologic responses to the injection. After the injection of a calcium-binding 1.5 ratio contrast agent, there is a decrease in the rate of myocardial uptake of glucose and lactate. This change persists for at least 20 minutes (Fig. 5).[15] These metabolic changes are consistent with impaired cellular oxidative metabolism or ischemia. However, they are not accompanied by detectable changes in either myocardial inotropic or cardiac electrophysiologic performance. Thus, their clinical significance must be considered uncertain. It is of interest, however, that this effect is either absent or there is actually a slight increase in lactate extraction when ventriculography is performed with a 3.0 ratio nonionic agent (Fig. 6).[16] It is unclear whether this means that 3.0 ratio nonionic agents have a clinically important metabolic superiority to calcium-binding 1.5 ratio agents. No studies have been performed examining the effects of noncalcium-binding 1.5 ratio or 3.0 ratio ionic contrast agents on this phenomenon.

PRIMARY EFFECTS ON CARDIAC CELLULAR ELECTROPHYSIOLOGY

There are 3 clinically important cardiac electrophysiologic effects of contrast agents: depression of sinoatrial nodal automaticity, depression of atrioventricular nodal conduction and increasing vulnerability to ventricular fibrillation.

Depression of sinoatrial nodal automaticity is responsible for the well-known sinus bradycardia that accompanies coronary angiography. This is caused by the combination of a direct effect of the contrast agent on sinoatrial nodal cells (which is not affected by autonomic blockade), and a reflex response elicited by intracoronary injection into sites that do not perfuse the sinoatrial node (abolished by autonomic blockade).[17] Calcium-binding 1.5 ratio agents cause the most marked effects, and 3.0 ratio nonionic agents cause the least marked effects (Fig. 7).[18] Noncalcium-binding 1.5 ratio agent formulations do not depress the sinoatrial node as much as calcium-binding formulations.[19]

Depression of atrioventricular nodal conduction is responsible for the transient heart block that may accompany the injection of contrast agent into the coronary artery that supplies the atrioventricular node. Like the effect on the sinoatrial node, the effect on the atrioventricular node is a combination of a direct effect and indirect autonomically mediated effects.[17] The relative orders of magnitude of the effects of the different classes of agents are similar to those for sinoatrial nodal function, with calcium-binding 1.5 ratio agents being most active, followed by noncalcium-binding 1.5 ratio agents and then 3.0 ratio ionic agents. The 3.0 ratio nonionic agents have the least activity (Fig. 8).[18]

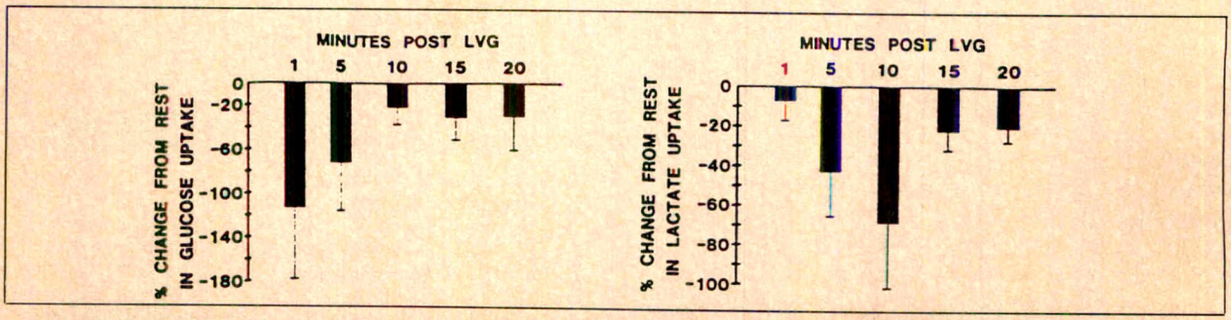


FIGURE 5. Time-related myocardial metabolic changes after left ventriculography (LVG) with Renografin 76. Values are expressed as mean percentage change from control. Note that myocardial glucose uptake *(left)* and myocardial lactate uptake *(right)* both decrease after injection and that the decrease persists for at least 20 minutes. (Reproduced with permission from *Am J Cardiol.*[15])

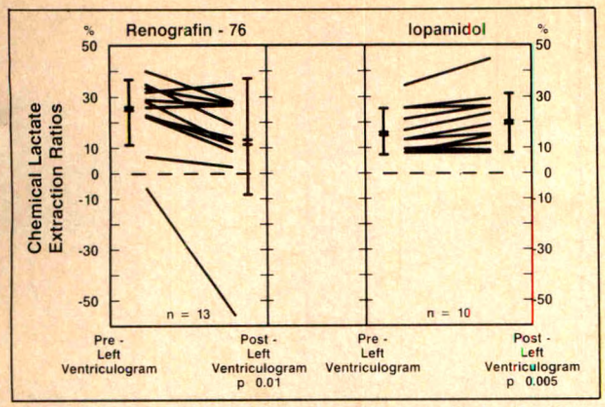


FIGURE 6. Myocardial chemical lactate extraction ratios before and after left ventriculography (LVG) with Renografin 76 *(left)* and with iopamidol *(right)*. Note that with Renografin 76 there is a significant decrease in lactate extraction ratio whereas with iopamidol there is a slight increase. (Reproduced with permission from *Am Heart J.*[16])

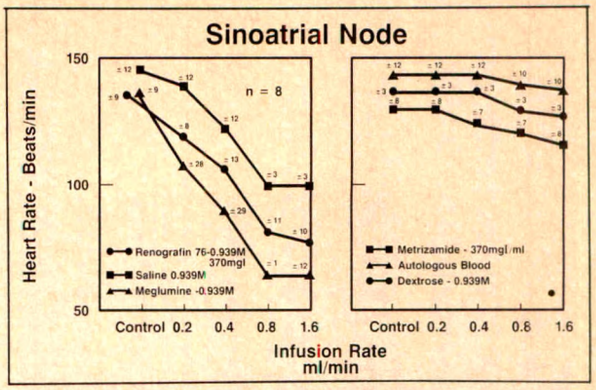


FIGURE 7. Effects on sinus rate of perfusion of the sinoatrial nodal artery at different rates with similar concentrations of various ionic *(left)* and nonionic *(right)* compounds. Note that the ionic compounds produce considerably more slowing than the nonionic compounds. (Reproduced with permission from *Radiology.*[18])

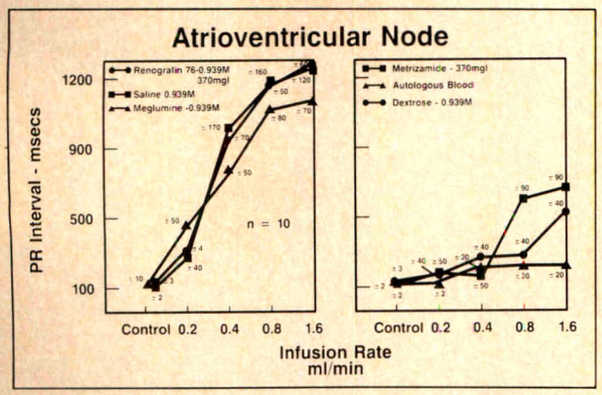


FIGURE 8. Effects on P-R interval as a measure of atrioventricular (AV) nodal conduction of perfusion of the AV nodal artery at different rates with similar concentrations of various ionic *(left)* and nonionic *(right)* compounds. Note that the ionic compounds produce considerably more depression of AV nodal conduction. (Reproduced with permission from *Radiology.*[18])

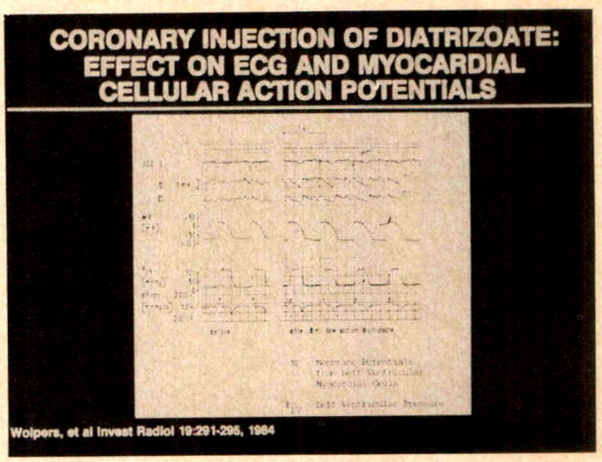


FIGURE 9. Recordings of body surface electrocardiogram (ECG), leads I, II, and III, left ventricular myocardial cell transmembrane potential (MP), left ventricular pressure (P_{LV}) and dP/dt in an open-chest dog. Recordings are made in the control state (before) and after the intracoronary injection of Urografin (a noncalcium-binding formulation of diatrizoate). Note that the injection causes hyperpolarization of the membrane during diastole and prolongation of the QT interval, which is due to prolongation of the ventricular myocardial cell action potential. dP/dt = a measure of left ventricular contractile state. (Reproduced with permission from *Invest Radiol.*[24])

Numerous studies using different experimental models have demonstrated that contrast agents increase the vulnerability to ventricular fibrillation, a property often measured as the ventricular fibrillation threshold.[20–23] The mechanism by which this occurs is not completely clear. Studies of ventricular myocardial cellular action potentials have demonstrated that intracoronary injection of contrast agents causes hyperpolarization of myocardial cells and prolongs action potential duration (Fig. 9).[24] Such a phenomenon, if it does not occur uniformly within the entire ventricular portion of the heart, could increase vulnerability to ventricular fibrillation.

Increased vulnerability to ventricular fibrillation begins within seconds after contrast agent injection and continues for approximately 45 to 60 seconds (Fig. 10).[20] Thus, the propensity for ventricular fibrillation persists for a period of time after the contrast agent has been cleared from the coronary vascular bed. Calcium-binding 1.5 ratio agents cause the greatest vulnerability to ventricular fibrillation, an effect that can be attenuated considerably by calcium enrichment (Fig. 11).[20,25] The 3.0 ratio ionic and nonionic agents and the noncalcium-binding 1.5 ratio agents similarly reduce ventricular fibrillation threshold (considerably less than that caused by the calcium-binding 1.5 ratio agents) (Fig. 12).[26]

PRIMARY EFFECTS OF INTRAVASCULAR VOLUME

The rapid intravascular injection of 50 ml of a contrast agent delivers a quantity of solute equivalent to that

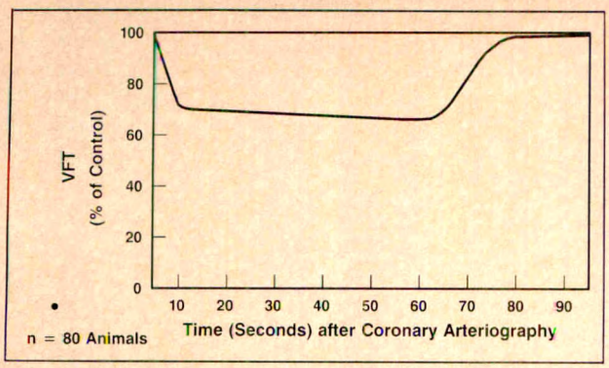


FIGURE 10. A time-averaged curve depicting the time course of reduction in the ventricular fibrillation threshold (VFT) after intracoronary injection of Renografin 76. Note that the increased vulnerability to ventricular fibrillation persists after the contrast agent has been cleared from the heart. (Reproduced with permission from *Invest Radiol.*[20])

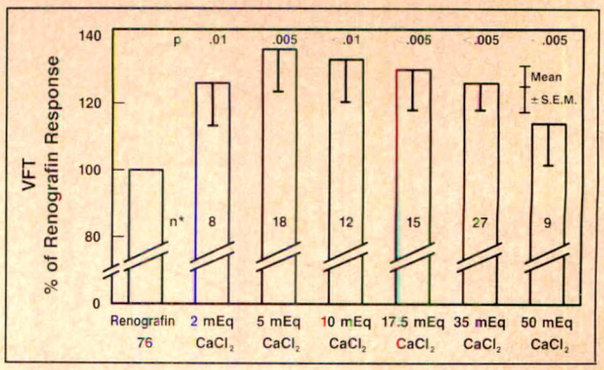


FIGURE 11. Effect of adding calcium chloride ($CaCl_2$) to sodium-methylglucamine iothalamate on ventricular fibrillation threshold (VFT). The values are normalized to the value evoked by Renografin 76. Note that at lower quantities of added calcium VFT is elevated but that this effect is reversed by larger quantities. S.E.M. = standard error of the mean. (Reproduced with permission from *Invest Radiol.*[20])

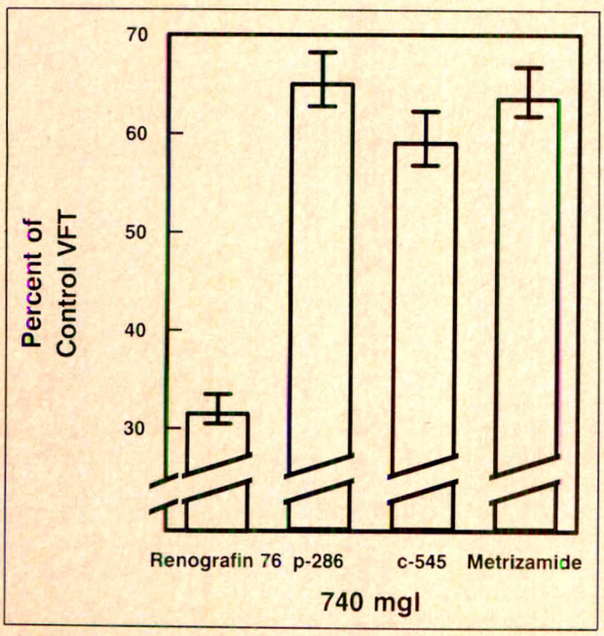


FIGURE 12. Comparison of the effects of selective intracoronary injection of a dose equivalent to 740 mg iodine of different ionic and nonionic contrast agents on reduction of ventricular fibrillation threshold (VFT). The mean values of VFT are expressed as a percentage of the control value. P-286 = ioxaglate; C-545 = iohexol. Note that the greatest reduction in VFT is caused by Renografin 76 and that the 3 3.0 ratio agents cause less reduction. (Reproduced with permission from *Invest Radiol.*[20])

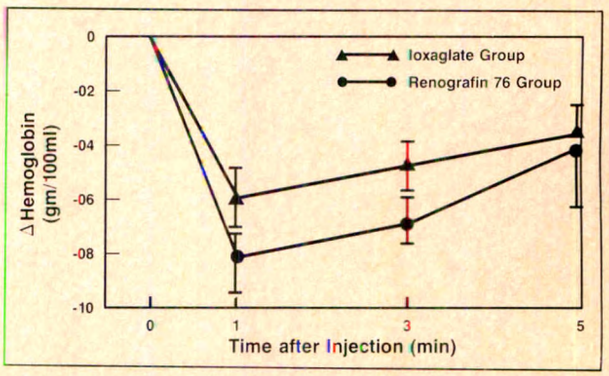


FIGURE 13. Comparison of the time-related change in whole blood hemoglobin concentration after left ventriculography with 45 ml of a 1.5 ratio contrast agent (diatrizoate) and a 3.0 ratio agent (ioxaglate). Note that the 1.5 ratio agent causes a greater decrease in hemoglobin, indicating greater blood volume expansion. (Reproduced with permission from *J Am Coll Cardiol.*[27])

contained in 100 ml (ioxaglate and ioversol 320 mg/ml iodine) to 250 ml (all 370 mg/ml formulations of diatrizoate) of blood plasma. Since the contrast agent molecule initially remains within the intravascular space, the injected solute draws water osmotically into the intravascular space, increasing the total blood volume. A portion of this water is derived from the red blood cells, but the majority comes from the extravascular compartment. This effect is reflected in a transient decrease in blood hemoglobin concentration (which averages 0.8 g/dl for 1.5 ratio agents and 0.5 g/dl for 3.0 ratio agents) caused by the acute expansion of intravascular volume (Fig. 13).[27] The duration of change in intravascular volume has not been studied. However, it would be expected to be transient since the contrast agent molecule rapidly gains access to the entire extracellular space and thus is no longer confined intravascularly.[28,29] Subsequently the contrast agent molecule is excreted in the urine, taking a certain quantity of water and electrolyte with it.

HEMODYNAMIC EFFECTS OF BOLUS INJECTION

The overall hemodynamic response to bolus injection of contrast agents is complex and is influenced by the interaction of 3 phenomena that differ in magnitude between the classes of agents. These are the effects on intravascular volume, the effects on myocardial contractile performance and the effects on systemic vascular

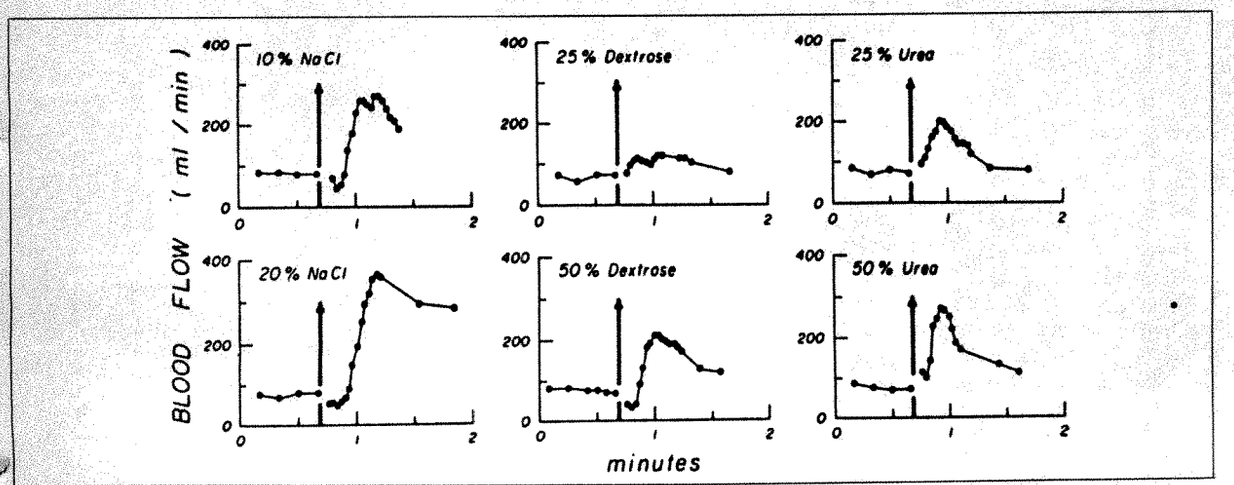


FIGURE 14. Effect of intraarterial injection of hypertonic solutions of different solutes on systemic arteriolar vasodilation. Note that vasodilation is a nonspecific dose-related response. NaCl = sodium chloride. (Reproduced with permission from *Am J Physiol.*[31])

resistance. The interaction among these phenomena is complex and the relative contribution of each may be difficult to separate from the others. However, the overall effects are well characterized.

Effects on systemic vascular resistance: All contrast agents cause systemic arteriolar vasodilation with onset coinciding with the arrival of the solution at the systemic microvasculature. This phenomenon is probably responsible for the sensation of warmth experienced during bolus injection of contrast agents.

The magnitude of the vasodilatory activity is directly related to the osmolality of each agent's formulation and the volume injected. It does not appear to be related to any pharmacologic property of the contrast agent molecule, but rather seems to be strictly a physiochemical phenomenon consistent with the known properties of any hypertonic solution of a pharmacologically inactive solute to cause systemic arteriolar dilation. Similar concentration-dependent phenomena have been observed during the systemic arterial injection of solutions of other pharmacologically inactive molecules such as glucose (Fig. 14).[30,31] Thus, the 1.5 ratio agents cause a greater degree of systemic vasodilation than the 3.0 ratio agents.

Effects on arterial pressure: The systemic arteriolar vasodilation produced by contrast agents causes a transient decrease in arterial pressure beginning within 10 seconds after bolus central injection. The arterial pressure generally bottoms out 30 to 45 seconds after injection and returns to baseline value within 60 to 90 seconds after the injection.[27,32] The decrease is frequently accompanied by a transient overshoot to a level above the preinjection value. The decrease is greatest for the 1.5 ratio agents and less for the 3.0 ratio agents (Fig. 15). The relative magnitudes of the changes caused by calcium-binding and noncalcium-binding 1.5 ratio agents have not been compared, while the relative magnitudes of the changes caused by ionic and nonionic 3.0 ratio agents are similar.[33]

Effects on left ventricular filling pressure: The acute expansion of intravascular volume, the action of some contrast agents to depress myocardial contractile performance and (if it occurs) the late overshoot of systemic arterial pressure combine to produce a transient elevation of cardiac filling pressures. The increase peaks 2 minutes after the injection and is mostly dissipated within 5 minutes. The magnitude of the increase in left ventricular end-diastolic pressure is greatest for 1.5 ratio agents (averaging 9 mm Hg) and less for the 3.0 ratio agents (averaging 4 mm Hg). The phenomenon also occurs on the right side of the heart but is of smaller magnitude and generally is of no clinical consequence.[27,32]

Effects on cardiac output: The combination of systemic vasodilation and increased intravascular volume causes an increase in cardiac output which, like the other changes, is related to the volume of contrast agent injected and the osmolality of the formulation. The increase is maximal 2 to 3 minutes after injection and resolves within 5 minutes. The 1.5 ratio agents evoke increases averaging

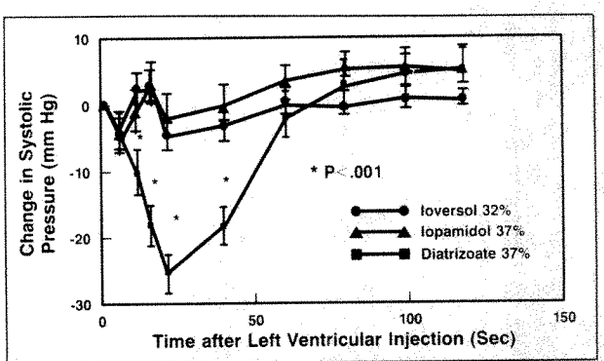


FIGURE 15. Comparison of the time-related change in systolic arterial pressure after left ventriculography with 45 ml of a 1.5 ratio contrast agent (diatrizoate) and 2 3.0 ratio nonionic agents (iopamidol and ioversol). Note that the 1.5 ratio agent causes a greater decrease in arterial pressure, probably because of greater systemic arteriolar vasodilation. (Reproduced with permission from *Am J Physiol.*[32])

0.8 liters/min, whereas the increases caused by the 3.0 ratio agents average 0.4 liters/min.[32]

EFFECTS OF SELECTIVE INTRACORONARY INJECTION

Hemodynamic effects: Selective intracoronary injection of contrast agents evokes a transient decrease in systemic arterial pressure that is maximal approximately 10 seconds after the injection. The effect is partially attributable to the direct myocardial effects of the different contrast agent formulations, and partially to a reflex response mediated by the injection.[34,35] The order of the magnitude of the effect of the different agents is as follows: calcium-binding 1.5 ratio agents (greatest effect), noncalcium-binding 1.5 ratio agents, 3.0 ratio ionic agents and 3.0 ratio nonionic agents. The latter cause little or no change in systemic arterial pressure.

Although the different classes of agents cause different magnitudes of changes in systemic arterial pressure, the differences between the agents are small compared to the hemodynamic effect of the held inspiration, which the patient generally performs during coronary arteriography. Thus, in general, differences between agents in their effects on arterial pressure are not clinically important.

Cardiac electrophysiologic effects: The aforementioned effects on sinoatrial nodal impulse formation and atrioventricular nodal conduction combine to produce a transient slowing of sinus rate and may either prolong atrioventricular nodal conduction or possibly produce transient atrioventricular nodal block immediately after selective intracoronary injection. The effect is more marked during right than left coronary injections.[36] The magnitude of all these effects caused by the 3.0 ratio agents is less than that caused by the 1.5 ratio agents.[37,38]

The role of contrast agents in provoking ventricular fibrillation during coronary arteriography has been the subject of considerable research. All studies demonstrate that ventricular fibrillation occurs most commonly when calcium-binding 1.5 ratio agents are used. The frequencies of ventricular fibrillation caused by noncalcium-binding 1.5 ratio agents and 3.0 ratio agents are less and are indistinguishable from each other. These findings are consistent with the differences in effects on cellular electrophysiology and ventricular fibrillation threshold between the classes of agents.

Two clinical studies have demonstrated that ventricular fibrillation occurs more frequently (95% confidence intervals 0.5 to 2.4%) when coronary arteriography is performed with Renografin 76 than when performed with Angiovist—a noncalcium-binding formulation of diatrizoate (95% confidence intervals 0 to 0.1%).[39,40] Three trials have compared the frequency of ventricular fibrillation during coronary arteriography with Renografin 76 to 3.0 nonionic agents. Both showed less ventricular fibrillation with the 3.0 ratio nonionic agents (Renografin 76 0.4 to 1.0%, iopamidol 0.06 to 0.4%).[41–43] One study that compared a noncalcium-binding formulation of diatrizoate (Urografin™) to iohexol and iopamidol reported no ventricular fibrillation in 287 procedures divided equally between the 3 agents.[44] However, this study had inadequate statistical power to demonstrate any existing difference.

These data demonstrate that there is an important difference between calcium-binding 1.5 ratio agents and all other agents in the frequency of ventricular fibrillation during coronary arteriography. However, there is probably little if any difference between noncalcium-binding 1.5 ratio agents and 3.0 ratio agents.

COMMENTS

Pharmacologic actions of currently used radiographic contrast agents are principally influenced by osmolality, sodium concentration and calcium-binding properties of their formulations. Within this framework, the calcium-binding 1.5 ratio agents have the most marked effects and the 3.0 ratio nonionic agents the least, with the noncalcium-binding formulations of 1.5 ratio agents and ioxaglate (the only 3.0 ratio ionic agent) in between.

From the hemodynamic point of view, the differences are predominantly related to osmolality, with the 3.0 agents causing less hemodynamic disturbance after bolus injection for left ventriculography. The magnitude of the difference is small enough that the 3.0 ratio agents have no important clinical advantage when used in patients with good or moderately impaired left ventricular function. However, in patients with severely impaired circulatory performance, the reduced hemodynamic stress associated with use of 3.0 ratio agents may confer a clinically important advantage.

The principal electrophysiological differences are between calcium-binding 1.5 ratio agents and all other agents, with clear-cut differences evident in the frequency of ventricular fibrillation during coronary arteriography. Thus, there appears to be no justification for use of calcium-binding 1.5 ratio agents. The 3.0 ratio agents appear to be electrophysiologically equivalent to noncalcium-binding 1.5 ratio agents and appear to cause less hemodynamic disturbance.

The circulatory reserve of most patients makes the differences between 3.0 ratio agents and noncalcium-binding 1.5 ratio agents clinically unimportant. In view of the substantial price disparity between 1.5 ratio and 3.0 ratio agents, it appears that noncalcium-binding 1.5 ratio agents are appropriate for patients with good circulatory performance and 3.0 ratio agents are best reserved for patients with impaired circulatory performance. The definition of the appropriate boundary between those patient groups requires further research.

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Experimental Contrast-Associated Nephropathy and Its Clinical Implications

George A. Porter, MD

Acute renal failure after contrast media injection has been recognized for at least 35 years but the exact mechanism responsible for the renal injury remains an enigma. The clinical characteristics of contrast-induced nephropathy (CAN) are well-known although more recently the nonoliguric presentation has occurred at an increased frequency—in 70 to 90% of cases. For nonoliguric presentation of CAN, one can expect an asymptomatic increase in serum creatinine, the mean peak occurring at 4.2 days. If oliguric, the fractional excretion of sodium will be <1% and resistant to either fluid challenge or loop diuretics. Preexisting renal insufficiency, with or without diabetes mellitus, increases the risk of CAN 6- to 10-fold but recovery is expected, with <10% of all patients requiring dialytic support. Despite the growing body of published reports, the lack of a suitable animal model to evaluate various proposed mechanisms of renal injury has compromised our ability to devise a technique for preventing CAN.

A popular scheme has been proposed to describe the possible sequence by which ischemia or nephrotoxins, or both, induce acute renal failure. In particular, a vascular mechanism (i.e., ischemia), is an appealing explanation for CAN since acute changes in renal hemodynamics after contrast media injection have been confirmed by several animal experiments. Unlike other vascular beds in which contrast media induce acute vasoconstriction followed by vasodilatation, the initial effect on the renal circulation is acute vasodilatation, followed by progressive vasoconstriction, increasing renal vascular resistance and a concomitant decrease in both renal blood flow and glomerular filtration rate. The intensity of the vasoconstrictive phase is reduced by either simultaneous volume repletion or pretreatment with a high-salt diet. However, these renal hemodynamic changes are short-lived, with complete return to normal within 1 to 2 hours after the procedure. Since clinically significant CAN involves continued deterioration of renal function for 3 to 10 days after the procedure, a more severe experimental renal insult is needed to mimic the clinical state. Examination of patients at risk for CAN (i.e., chronic renal insufficiency, diabetic nephropathy, congestive heart failure and hypertension) reveals that preexisting renal ischemia is a common association. Under these circumstances, renal ischemia will induce stimulation of both endogenous vasoconstrictors (angiotensin II, norepinephrine and vasopressin) and vasodilator substances (prostaglandin I_2 [PGI_2] and prostaglandin E_2 [PGE_2]). A disturbance of this balanced vasoconstrictor/vasodilator action on renal circulation will cause acute deterioration of renal function.

Animal experiments suggest that contrast agents act in a manner similar to nonsteroidal anti-inflammatory agents by selectively inhibiting the vasodilatation caused by prostaglandins and inducing renal dysfunction. Circulating angiotensin II causes both renal vasoconstriction, principally in the efferent arterioles, and de novo synthesis of vasodilator prostaglandins. In the unstimulated state, circulating angiotensin II induces a balanced state between constriction and dilatation resulting in normal renal vascular resistance. When renin release is stimulated, the associated increase in angiotensin II results in increased vasoconstrictive and vasodilatory actions, with the final effect on renal vascular resistance being either unchanged or modestly increased. However, selective interference with the prostaglandin limb of the stimulation causes a reduction in renal blood flow, and the possibility of a reduction in glomerular filtration rate. From animal studies one of the effects of contrast media is to interfere with PGI_2 production, thus resembling nonsteroidal antiinflammatory drugs with regard to the pathophysiologic process leading to acute renal failure.

(Am J Cardiol 1990;66:18F–22F)

The association between contrast media and acute renal failure can be traced back to the early 1930s.[1] In a survey of radiologists in the United States and Canada reporting more than 660,000 urographic examinations, 26 deaths were tabulated, 12 occurring within 24 hours, while the remaining 14 deaths were delayed anywhere from 1 to 25 days after the radiographic procedure. In the latter group of delayed deaths, 6 patients died of uremia. Pendergrass et al[1] pointed out that preexisting renal impairment was present in many of the patients who subsequently died of uremia. Furthermore, since infection complicated several of the uremic patients, they concluded that concomitant treatment with sulfadiazine could have contributed to the renal damage.

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This survey also contained a review of 11 previous deaths that had been reported in association with contrast media.[1] Of these 11 patients, 3 had uremia as a complication and in 1 case it was considered to be secondary to a "toxic" nephrosis.[2]

The first clear connection between contrast media and acute renal failure was reported by Bartels et al[3] in a patient with myelomatosis. Despite these disquieting observations, in 1963 Schwartz et al[4] reported the successful use of high-dose intravenous urography to evaluate patients with renal insufficiency without apparent adverse consequences. With reassurance that the procedure was tolerated in the presence of chronic renal failure, contrast studies were conducted in patients with significant renal impairment in increasing frequency and, as reported by Webb et al,[5] by the late 1970s the number of reported cases of acute renal failure after intravenous urography had mounted, reaching almost 80 cases in 1978. Since these cases alerted both the radiologic and nephrologic communities to this adverse reaction, there have been numerous reports defining the incidence and stratifying the risk factors for the development of contrast-associated nephropathy (CAN).[6] Despite this accumulation of clinical data, the exact mechanism responsible for the renal injury associated with contrast media remains an enigma.

CLINICAL PRESENTATION OF CONTRAST-ASSOCIATED NEPHROPATHY

The characteristic clinical presentation of CAN has been described in detail.[7-9] Whereas <10% of cases reported by Byrd and Sherman[7] were nonoliguric, more recent prospective studies[10,11] have reported that a nonoliguric renal failure occurs in the majority of cases. An increase in serum creatinine is temporally related to the use of contrast media and occurs within the first 24 hours after the procedure.[9] Although serum creatinine is stated to peak by the third day after the procedure,[6,7] a review of a series of studies in which serum creatinine was followed to peak[12-18] allows the calculation of a mean of 4.2 days after the procedure to achieve peak serum creatinine.[9] While the most frequently used criterion for CAN is a 1 mg/dl increase in serum creatinine over baseline occurring within 48 hours,[19] based on the delayed peak in many patients, such a criterion will result in underreporting the number of cases involved. Conversely, if one applies a criterion of a 25% increase above baseline for serum creatinine of ≤1.5 mg/dl or a 1 mg/dl increase above baseline for serum creatinine >1.5 mg/dl at 72 hours after the procedure, or both, one is assured of identifying all patients who show renal dysfunction after contrast media injection.[9] While an increase in the formed elements in the urine frequently occurs in cases of CAN, these changes are nondiagnostic and do not correlate with renal dysfunction after the injection of contrast media.[20] Fang et al[21] reported 12 patients with oliguric renal failure due to CAN in whom the fractional excretion of sodium was <1%. Based on these findings, they argued for a vascularly-mediated cause of acute renal failure.[21] However, similar measurements by Shafi et al[17] failed to categorize CAN as an oliguric acute renal failure characterized by a low fractional sodium excretion. A persistent nephrogram 24 hours after contrast injection has been considered to be a highly specific but insensitive measure of CAN.[22] Thus, given our current information, it would appear that the clinical presentation of CAN involves the asymptomatic increase of serum creatinine occurring within 24 hours of a contrast study with or without associated oliguria and occurring in greater frequency in patients at high risk (i.e., patients with significant impaired renal function with or without associated diabetes).[8] Fortunately, recovery is to be expected in such patients, with <10% requiring dialytic intervention.[6] Despite the growing body of published reports, the lack of a suitable animal model to evaluate various proposed mechanisms of renal injury has compromised our ability to devise a technique for the prevention or modification of CAN.

PROPOSED MECHANISM

Figure 1[23] outlines a popular scheme regarding the possible mechanism by which renal ischemia or nephrotoxins, or both, induce acute renal failure. Since renal function is dependent on 2 major processes—perfusion/filtration and reabsorption/secretion—acute renal injury is considered to have a dual mediation through both reduction in blood flow and tubular injury. In those instances where the vascular effect predominates, the result is a change in both renal blood flow and the glomerular filtration coefficient (K_f), which leads to a reduction in the physical forces responsible for filtration; this causes a reduction in the glomerular filtration rate and a subsequent retention of the normally filtered blood components. On the other hand, tubular injury can lead to both a direct change in cell membrane permeability or integrity, or both, with a resulting loss of the selective permeability characteristics of the cell and the backleak of filtration markers plus the possibility of interluminal obstruction, leading to a reduction in the physical forces responsible for driving the filtration rate. The net effect of these adverse effects on nephron integrity is an overall reduction in glomerular filtration rate that is clinically evident by the increase in serum creatinine.

Of the possible factors contributing to CAN, vascular mediation (i.e., ischemia) has particular appeal, since the acute changes in hemodynamics that consistently follow the injection of contrast media have been confirmed by several investigators using a variety of experimental animals.[24-28] Unlike other vascular beds in which contrast media induce acute vasoconstriction followed by a prolonged vasodilatory phase, the initial effect of contrast media on the renal circulation is acute vasodilatation followed by progressive vasoconstriction, with an increase in renal vascular resistance and a concomitant decrease in both renal blood flow and glomerular filtration rate.[24-28] The suggested mediators of this renal vasoconstriction have included the renin-angiotensin system, interference with the synthesis of renal prostaglandins and a transcellular relocation of extracellular calcium ion.

The role of the renin-angiotensin system was examined in the salt-restricted dog by Larson et al.[28] In the

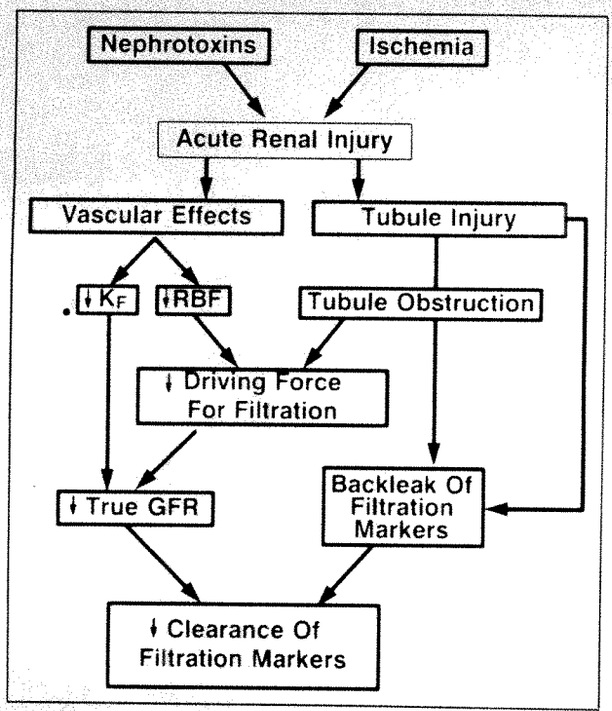


FIGURE 1. Pathophysiology of acute renal failure. Reduction in filtration markers occurs with either ischemia or nephrotoxins. The net effect occurs through either a reduction in glomerular filtration rate (GFR) or a loss of tubular integrity. K_f = glomerular filtration coefficient; RBF = renal blood flow. (Reproduced with permission from *Clinical Nephrology*.[23])

presence of a stimulated renin-angiotensin system, via sodium depletion, the investigators were able to demonstrate an exaggerated vasodilatory and vasoconstrictor response after direct intraarterial injection of contrast media. Furthermore, pretreatment with saralasin decreased the magnitude but did not eliminate the occurrence of the vasoconstrictor phase. Subsequent sodium repletion also blunted the magnitude of the biphasic renal vascular response. This finding was contrary to observations reported by Katzberg et al[29] but was compatible with the earlier report of Caldicott et al.[30] Lund et al[31] pretreated anesthetized dogs with buffered acetylsalicylic acid, which caused a lowering of precontrast renal blood flow but did not attenuate the contrast-induced biphasic fluctuations in renal blood flow. The latter investigators concluded that the acute hemodynamic alterations induced by radiocontrast media were not mediated by renal prostaglandin production. Bakris and Burnett,[32] using an anesthetized dog model without sodium restriction, investigated the role of extracellular calcium as an important mediator of radiocontrast-associated changes in renal blood flow and glomerular filtration rate. After pretreatment with either verapamil, diltiazem or ethylene glycol-bis-(β-aminoethyl ether)-N,N′-tetraacetic acid (EGTA) infusions, response to contrast media included an exaggerated initial vasodilatory response to the interarterial injection, while the late vasoconstrictive phase was eliminated.[32] There was no effect on baseline renal blood flow with these calcium modifying agents, but there was a significant 20% reduction in glomerular filtration rate, which preceded the injection of contrast media. The possible influence of pretreatment with either calcium antagonists or EGTA on perfusion characteristics of the glomerular vessels, given this measurable change in filtration fraction, raises a question as to the proper interpretation of their findings.

The intensity of the vasoconstrictive phase after acute contrast media injection can be reduced by either simultaneous volume repletion[26] or by pretreatment with a high-salt diet.[28] However, these changes in vasoactivity are short-lived, with complete restoration of renal hemodynamics within 1 to 2 hours after the procedure. Since clinically significant CAN involves continued deterioration of renal function for 3 to 10 days after the procedure,[16] a more severe experimental renal insult is needed to mimic the clinical condition. When one reviews the profile of patients at risk for CAN (i.e., those with chronic renal insufficiency, diabetic nephropathy, congestive heart failure and hypertension),[9] preexisting renal ischemia is a shared feature. Carried a step further, such ischemia is often associated with the stimulation of both endogenous vasoconstrictors (angiotensin II, norepinephrine and vasopressin) and vasodilator substances (prostaglandin I_2 [PGI_2] and prostaglandin E_2 [PGE_2]). Support for the important role of simultaneous vasodilator/vasoconstrictor activation comes from recent animal studies. Heyman et al[33] were able to induce acute renal failure after injection of contrast media in salt-depleted rats pretreated with uninephrectomy and indomethacin; the latter maneuvers resulted in a state of renin-angiotensin stimulation with the inhibition of prostaglandin synthesis. Vari et al,[34] using salt-depleted rabbits, were able to induce experimental acute renal failure with the combination of indomethacin and contrast media. Again, the combination of a stimulated renin-angiotensin system coupled with prostaglandin inhibition through pharmacologic blockade of cyclooxygenase caused a temporal pattern of acute renal failure resembling that seen in clinical acute oliguric renal failure. Of equal interest is the observation of Workman et al[35] reporting that PGI_2 production was significantly inhibited for up to 1 hour after a bolus injection of contrast media in the dog; this occurred in the setting of increasing renin production. Thus, current animal models simulating CAN have as their common denominator the induction of a degree of renal ischemia with the net effect of a significant alteration in the resting state of glomerular hemodynamics.

Endogenous vasoconstrictors are known to have a selective action on the arteriolar network of the glomerulus.[36] While norepinephrine has a vasoconstrictive effect on both the afferent and efferent arteriole, the vasoconstrictive actions of angiotensin II are limited to the efferent arteriole. Renal prostaglandins (such as PGI_2) counteract the intrinsic vasoconstrictive effect and thus serve to restore renal autoregulation. By eliminating the intrinsic vasodilating effect of the prostaglandins, as occurs during cyclooxygenase inhibition, glomerular filtration pressure is maintained at the expense of a reduced postglomerular blood flow. Contrast media have their adverse

consequences in this setting.

The data of Heyman and co-workers[33] indicate that the thick ascending limb of the nephron is the most vulnerable segment for oxygen deprivation. Whether histologic tubular necrosis occurs versus a reversible renal dysfunction is probably due to the magnitude of the insult and the coexisting degree of renal vasoconstriction. Thus, it is predictable that CAN would present clinically as a spectrum ranging from simple dysfunction, characterized by a transient elevation in serum creatinine, to a profound oliguric renal failure, which would require dialysis support for the patient's survival.

Other mechanisms that could complement the renal dysfunction noted in contrast nephropathy would include direct tubular toxicity. Moreau and colleagues[37] have reported histologic observations in the proximal tubule after contrast media administration that include the following: vacuolization, interstitial edema and tubular degeneration. Additional evidence of direct tubular effects of contrast media come from the documented reduction in para-amino-hippuric (PAH) acid extraction associated with contrast injections into the renal artery,[38,39] an effect that is not evident with injections of hyperosmolar solutions of either mannitol or saline. Enzymuria, which regularly follows contrast injections, is of great interest.[40,41] These enzymes originate from both brush border and cell cytosol. However, interpretation of enzymuria as a marker of renal cell injury remains to be established.

An early proposed mechanism for CAN was that of intraluminal obstruction secondary to the precipitation of contrast media with various urinary protein components. This was proposed in cases of multiple myeloma,[42] and more specifically associated with Tamm-Horsfall mucoprotein.[43] Unfortunately, there has been no conclusive proof that such precipitation occurs in vivo. Furthermore, micropuncture results from animal models of CAN failed to substantiate an elevation of intertubular pressure but did document a significant reduction in K_f.[34] Because contrast agents are known to have uricosuric properties, it has been suggested that CAN may actually be a manifestation of hyperuricemic acute renal failure.[44] However, when this mechanism was specifically evaluated[20] it was not proven to be of etiologic significance.

While Vari et al[34] were unable to protect the rabbit against CAN by using either mannitol or diuretics, pretreatment with desoxycorticosterone acetate and saline drinking water sufficient to suppress plasma renin activity stimulation did prevent the development of the anticipated contrast-induced renal injury. Whether associated use of calcium antagonists will also protect against acute renal failure remains a matter of speculation.

In summary, there is a striking parallel between the conditions required for the induction of experimental CAN and the proposed mechanism by which nonsteroidal antiinflammatory agents induce their hemodynamically mediated renal dysfunction.[45] Figure 2 is a schematic of a proposed mechanism for nonsteroidal antiinflammatory drug-induced renal dysfunction.[45] Circulating angiotensin II initiates both a vasoconstrictor effect on renal vessels and de novo synthesis of vasodilatory prostaglandins. In the basal state (Fig. 2A), low levels of circulating angiotensin II provide a balanced state of both vasoconstriction and vasodilatation, resulting in a normal renal vascular resistance. In states where renin is stimulated (Fig. 2B), the associated increase in angiotensin II again results in an increase in both vasoconstrictive and vasodilatory actions with the final effect on the renal vascular resistance being one of either unchanged or modest increase. However, as is shown in Figure 2C, selective interference with the prostaglandin limb of the stimulation, as might occur with indomethacin administration, results in a net increase in renal vascular resistance causing ischemia, a reduction in renal blood flow and a possible corresponding reduction in glomerular filtration rate. If one of the effects of contrast media is to interfere with prostaglandin production, as is suggested by the experiments of Workman et al,[35] then the mechanism causing CAN would resemble that of nonsteroidal antiinflammatory drugs by causing the interruption of the physiologic counterregulatory process mediated through prostaglandin stimulation, and thus lead to acute renal dysfunction. If there were coexisting changes in the renal vascularity of a structural nature, then the intensity of the vasoconstriction produced by contrast media could be profound enough to have a significant injurious effect on renal tubules, a condition that resembles the experiments of Heyman et al.[33] While the cause of CAN remains to be eluciated, the development of experimental models will assist us in unravelling the pathophysiology of this entity and providing a framework for developing preventive measures to eliminate this adverse consequence of an exceedingly useful and important diagnostic technique.

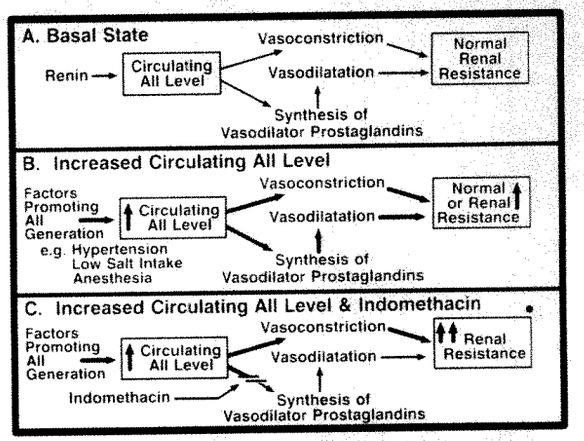


FIGURE 2. Interaction of the angiotensin II (AII) and prostaglandins on the regulation of renal hemodynamics. See text for details. (Reproduced with permission from *Am J Med.*[45])

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A Hematologist's View of Contrast Media, Clotting in Angiography Syringes and Thrombosis During Coronary Angiography

Eric F. Grabowski, MD, ScD

While ionic contrast media (CM) are stronger anticoagulants and antiplatelet agents, both nonionic and ionic CM retard clotting, fibrinopeptide A generation and platelet aggregation (at least by Born-O'Brien aggregometry). Thus, nonionic CM do not cause clots and thrombi. Rather, the driving force for clot or thrombus formation, when it occurs, is blood contact with and activation by the foreign surface of a syringe or catheter itself. A marked enhancement of clotting by glass syringes in comparison to plastic ones supports this view. Blood in any syringe or catheter, therefore, will clot more slowly in the presence of nonionic or ionic CM, the inhibitory effects of the latter being more profound. With respect to models of thrombosis at sites of vascular injury or stenosis, the antithrombotic effects of CM may either be transient owing to the dynamic nature of blood flow (local endothelial cell denudation model), or as in the case of ionic CM, actually to enhance local platelet aggregation (stenosis model). In these situations, preservation of the antithrombotic functions of endothelium with nonionic CM may be quite critical.

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A recent prospective study involving more than 300,000 patients receiving contrast media (CM) has clearly demonstrated that the incidence of severe adverse reactions is much lower for nonionic media than for ionic media.[1] Serious adverse reactions in this study were defined as dyspnea, sudden decline in blood pressure, cardiac arrest, loss of consciousness requiring some form of physician intervention, or a combination of these factors. As a result of this and other investigations, low osmolar (chiefly nonionic) CM were used in 70% of cardiac arterial procedures in 1989. Universal adoption has not occurred chiefly because of the much greater initial cost of such CM; studies of the long-term cost-effectiveness of nonionic CM are in progress.

A controversy in a different arena, however, threatens the continued use of nonionic CM in cardiology and neuroradiology: blood coagulation. There have been reports[2–4] that nonionic CM not only are weaker anticoagulants than ionic CM, but also actively promote clotting in catheters and angiography syringes, thereby placing patients at risk of thromboembolism. Therefore, we address 2 questions: (1) Do nonionic CM present a clotting hazard when angiography syringes are contaminated with aspirated blood? And (2), do nonionic CM afford as much protection as ionic CM against sudden platelet thrombosis at sites of local vascular injury and coronary artery stenoses? From the standpoints of the fields of biomaterials, blood rheology, and clotting and thrombosis, we find the case for the continued use of nonionic CM to be the stronger one.

CLOTTING IN ANGIOGRAPHY SYRINGES

We evaluated 2 nonionic (iohexol 370 and iopamidol 350) and 2 ionic (ioxaglate 320 and diatrizoate) contrast agents by comparing their potential to affect clotting in 420 angiography syringes made of plastic (polypropylene) or glass. In follow-up to an earlier study by Englehart et al[2] we used a blood-contrast media ratio of 2 ml: 5 ml and 10 donors, each of whom was studied at 4 time points. However, in contrast to that study, we used earlier time points to assess clotting (10, 20, 30, and 60 minutes), normal blood donors rather than patients, a parallel study of clotting and fibrinopeptide A (FPA) generation in plastic tubes and life-table analysis to estimate more accurately donor-based early clotting probabilities. We found that while ionic CM are stronger anticoagulants, both nonionic and ionic media retard clotting in plastic tubes, and clotting in plastic and glass angiography syringes in comparison to saline controls.[5] In particular, a clotting probability of 1% for nonionic agents in plastic

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TABLE I Properties Associated with Thromboresistance of Biomaterials

Hydrophobicity	Ordered structure
Hydrophilicity	Surface smoothness
High surface-free energy	Surface roughness
High net negative charge	Porosity
Critical surface tension	Surface chemical conformation
High crystallinity	Surface molecular chain mobility

TABLE II Materials Used for Catheters

Polydimethylsiloxan (Silastic)
Polyethylene
Expanded polytetrafluoroethylene (e PTFE, Teflon)™
Polyvinylchloride
Polyurethanes

syringes was not reached until a time (mean ± standard deviation) of 21.4 ± 3.2 minutes. This contrasts with a time of 8.7 ± 2.5 minutes for saline controls. With plastic syringes, no clotting at all was observed at 10 and 20 minutes with either class of agent (total of 80 syringes). On the other hand, both classes of agent were associated with clotting if one waited long enough (5 of 40 plastic and 12 of 40 glass syringes containing ionic media and incubated for 30 or 60 minutes). Neither class of agent, further, hastened the generation of FPA, levels of which even for saline controls remained not different from baseline for at least 4 minutes. Thus, nonionic CM do not cause clots and are not procoagulant.

Bull et al[6] believe that a qualitative, and not just a quantitative difference exists in the anticoagulant potency of nonionic and ionic CM. They base this belief chiefly on the absence of any clots with ionic CM in the study of Englehart et al.[2] Our data support a different view: at 30 and 60 minutes clots were indeed seen with ionic media in both plastic and glass syringes. We believe that Englehart et al did not observe such clots largely because in their study bloods were drawn through femoral arterial catheters that likely had been prefilled if not also flushed with a heparinized solution, as is standard catheterization laboratory practice.

ROLE OF FOREIGN SURFACE PROPERTIES

When clot formation in a syringe or catheter does occur, the driving force is blood contact with the foreign surface of the syringe or catheter itself, as is well recognized in the field of biomaterials.[7] Table I summarizes some of the many biomaterial properties considered important in this area, while Table II lists some of the specific materials used in catheters today. The marked enhancement of clotting by glass syringes in comparison to plastic ones noted by both Englehart et al[2] and us[5] supports this point of view. Were foreign surface properties unimportant, such a glass-plastic difference would be inexplicable.

Thrombus formation in arterial catheters, further, has been commonly observed in the complete absence of contrast media. In a prospective study of 81 newborns with umbilical artery catheters, for example, Siebert et al[8] used 2-dimensional ultrasonography to demonstrate the presence of clots or thrombi at or near the tips of catheters in 21 of these infants. In other reports[9,10] the incidence of such clots in newborns ranged from 10 to 90%.

Specific foreign surfaces may even make evident species differences in platelet adhesion. We have observed[11] that the adhesion of human platelets to cuprophane and polyurethane under controlled conditions of whole blood flow is orders of magnitude less than that for canine or rabbit platelets. This observation may help explain why Hwang et al[4] found an incidence of dog thromboembolism with nonionic CM of 100% (5 of 5 animals), vs a 0.15% incidence in a representative human study based on 7,230 patients.[12]

PLATELET ADHESION/AGGREGATION

We studied the effects of CM on platelet adhesion/aggregation at a site of injury to vascular endothelium in an in vitro system designed to simulate coronary blood flow. Our experimental system comprised a parallel-plate flow chamber, 1 surface of which was a monolayer of bovine aortic endothelial cells previously grown to confluence on a number 1 cover glass, an epifluorescence videomicroscope, an image intensifier and an image processor permitting online and offline digital image processing.[13,14] Blood was collected by venipuncture into 3.8% sodium citrate (9 parts blood to 1 part citrate) from each of 4 healthy donors, none of whom had taken aspirin or other antiplatelet medication in the preceding 10 days. The blood was then incubated for 45 minutes on a rocker with the thrombasthenia (TAB) murine monoclonal antibody to platelet glycoprotein IIB (courtesy of Dr. R. McEver, University of Oklahoma Medical Center), incubated for another 45 minutes with a fluorescein-conjugated goat anti-mouse antibody, and placed in a gently-stirred beaker maintained at 37°C by a water bath. To aliquots of blood were added 20% by non-red cell volume saline, iohexol 370, ioxaglate 320, or diatrizoate. A withdrawal pump drew blood from the beaker via a heat exchanger (to maintain 37°C) and through the chamber at 1.0 ml/min (coronary artery-like shear rate of 270 seconds^{-1}). From video recordings we calculated at time 5 minutes: (1) percent platelet coverage of an 80 μm wide area of monolayer denudation introduced just before a given experiment; (2) mean thickness of individual platelet aggregates at this site; and (3) volume of adhesion/aggregation. In general, platelet adhesion/aggregation was a dynamic process characterized by platelet turnover confined to the injury site. Net platelet adhesion/aggregation increased with time and, in parallel studies, passed through a maximum with respect to increasing shear rate.

When endothelial cell monolayers had seen no CM before blood flow but CM was present in the flowing blood, all 3 parameters of platelet adhesion/aggregation were significantly ($p < 0.01$ to 0.05) reduced for ionic CM. The data suggested milder reductions for iohexol. These results agree with findings in the Born-O'Brien aggregometer, for which both classes of CM have already

been shown to inhibit platelet function.[15] However, when monolayers had been incubated with complete culture medium containing 20% CM for 10 minutes before blood flow, but no CM was present in the flowing blood, platelet adhesion/aggregation was not significantly reduced by any agent (Table III). This latter situation can be likened to the rapid dispersal by blood flow of a bolus of CM away from a site of vessel disease or injury. In agreement with these findings are studies of Born-O'Brien aggregation performed at the beginning and at the end of routine cerebral angiography, which show that platelet inhibitory effects of CM, clearly observed in parallel in vitro studies, are almost completely diluted in the general circulation.[15] Similarly, platelet aggregation studies performed on blood taken from 42 patients, each of whom received 100 to 300 ml of CM, revealed that platelet function in mixed venous blood is unaffected by either class of CM (Kiramatsu K., personal communication). Any benefits of greater inhibition of platelet function by ionic CM, therefore, are short-lived in flowing blood.

TABLE III Platelet Adhesion/Aggregation with Contrast Media Before Blood Flow

Contrast Media	% Plt Coverage	Mean Aggregate Thickness (%)	Volume of Ad/Agg (%)
Saline	35 ± 3.9	100	100
Iohexol	30 ± 6.1	64 ± 15	70 ± 24
Ioxaglate	27 ± 4.0	74 ± 20	61 ± 19
Diatrizoate	28 ± 1.1	59 ± 15	53 ± 22

Ad/Agg = adhesion/aggregation; Plt = platelet.

MODEL FOR CORONARY ARTERY STENOSIS

In an alternative flow chamber we have simulated blood flow past a stenotic lesion (Fig. 1). The lesion itself is a lucite insert measuring 1.6 mm in the direction of flow that fits by friction into the chamber base. Microfibrillar collagen is preadsorbed onto the chamber's uppermost face, which lies 100 μm from a monolayer of human umbilical vein endothelial cells. Degree of flowpath obstruction is therefore [290 μm − 100 μm]/290 μm × 100 = 66%, which is characteristic of a relatively high-grade lesion. The 1.6 mm axial dimension is typical of coronary lesions seen in fresh postmortem adult hearts.[16] In initial experiments with saline (20% by non-red cell volume), the intense platelet reactivity of the "lesion" results in numerous lesion-adherent platelet aggregates measuring 100 to 300 μm in diameter. Contributing to this reactivity are locally high shear rates, which maximize delivery of fresh platelets.[17] With CM, aggregate size is reduced by iohexol 370, but paradoxically increased by ioxaglate 320 and diatrizoate. Parallel observations carried out with transmitted light videomicroscopy suggest that in the latter case nonplatelet material (endothelial cells?) makes up large portions of the apparent aggregates. In this model of more severe vessel-wall injury, therefore, ionic CM may lead to a greater local thrombotic risk.

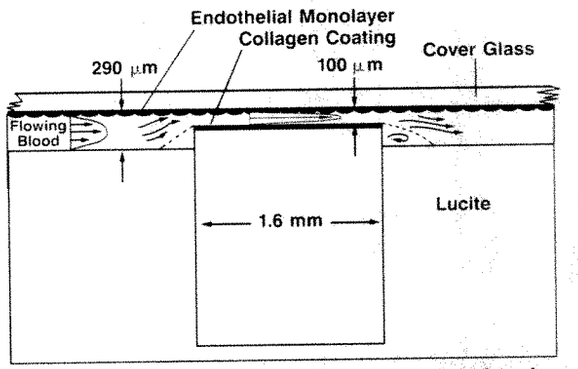


FIGURE 1. Cross-section of flow chamber developed to simulate blood flow past a stenotic lesion.

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Selection of a Contrast Agent in the Cardiac Catheterization Laboratory

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The evolution of contrast material for intravascular use has been directed toward the development of better-tolerated agents. Currently, a variety of such "dyes" are available for coronary angiography and left ventriculography. Considerable animal and human investigation suggests that significant differences exist between the families of contrast agents that relate to patient tolerance. The newer low osmolality agents (especially the nonionic agents) produce less perturbation of the homeostatic state, which is clinically manifested by a lessened incidence of side effects, including those of a hemodynamic and electrophysiologic nature. While controversy continues over the cost/benefit ratio of the low osmolality contrast agents compared to traditional high osmolality agents, the former are rapidly becoming the community standard for diagnostic and especially therapeutic cardiologic procedures. Accepting the advantages of the low osmolality contrast agents, differences between the ionic dimers and the nonionic agents have been examined. Both experimental and clinical data suggest superiority of the nonionic agents. Although controversy still surrounds the issue of thromboembolism with the nonionic agents, accumulating evidence fails to support a clinically significant relation.

The choice of contrast material is the responsibility of the invasive cardiologist. While the benefits of low osmolality agents are most obvious in high-risk patients, experience with large-scale intravenous studies suggests that the choice of contrast agent is a better discriminator of adverse reaction than is preprocedural risk stratification.

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Within months of Roentgen's discovery, x-rays were used to visualize blood vessels in anatomic specimens on intravascular injection of a radiopaque substance.[1] While the agents initially used were toxic, postmortem angiography proved to be a valuable teaching tool before the development of a clinically acceptable contrast material. The first in vivo human angiogram is credited to Heuser, who reported in 1919 the use of potassium iodide to opacify the veins of an upper extremity.[2] Over the ensuing years, intravascular administration of a variety of agents including Lipiodol, strontium bromide and thorium was evaluated, and each was found to have significant toxicity. In 1929 an organic iodide, Uroselectan, was developed for use in intravenous urography. This agent was better tolerated than its predecessors and led to the synthesis of a number of other agents including Iopax, Neo-Iopax, Skiodan, Diodrast and Urokon. Beginning in the middle of the 1950s, fully substituted triiodinated benzoates (diatrizoate, iothalamate and metrizoate) were introduced; these soon became the media of choice for angiography and have remained so for almost 25 years. While these agents are reasonably well tolerated, they have been associated with untoward reactions varying from the minor subjective complaints of discomfort to catastrophic cardiovascular collapse and death.

Toxicity of these "traditional" contrast materials has been attributed to high osmolality, specific anions and cations comprising the compound, and nonradiopaque additives. Even so, physicians have grown accustomed to these agents and accepting of their limitations such that they are hardly considered drugs but rather inert substances used for transient illumination of otherwise invisible structures.

Within the past 10 years, a number of intravascular contrast agents with lessened osmolality have been introduced purporting to be better tolerated and perhaps safer than the high osmolality ionic agents. In a variety of animal and human studies, these agents have consistently demonstrated lessened perturbation of physiologic parameters. While the quality of many of these studies has been debated,[3] most angiographers agree that low osmolality media (LOM) appear advantageous. The primary drawback of the latter is increased cost, which is 15 to 20 times that of high osmolality media (HOM). This has led some to question the cost-benefit ratio of the LOM, suggesting the need for a well-structured, large scale, randomized, controlled trial.[4]

While most radiologists appear to believe that LOM offer benefits in terms of patient care, they have been reticent to use them because of cost.[5] Cardiologists have been quicker to adopt the LOM, currently using them in

70% of the diagnostic and 80% of the therapeutic procedures done in the United States (Fig. 1). The reasons for this include the obvious differences in electrocardiographic and hemodynamic effects between HOM and LOM, the greater morbidity and mortality of coronary angiography and the relatively small contribution of contrast media to the overall expense of the procedure. Controversy remains as to whether the benefits gained by routine use of LOM in the catheterization laboratory justify the cost and whether differences among the LOM favor the use of one over another. The purpose of this discussion is to establish a perspective from which to view the contrast materials currently available for angiography.

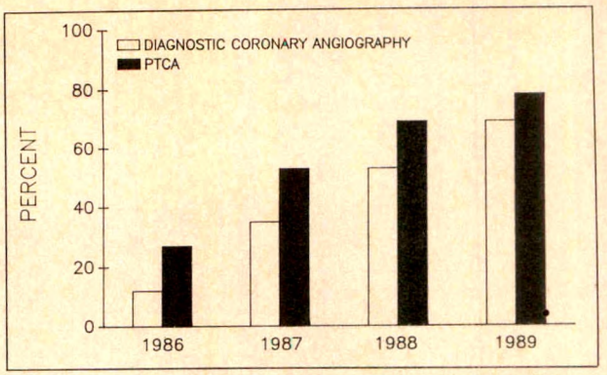


FIGURE 1. Use of low-osmolality contrast media in cardiology in the United States from 1986 to 1989. PTCA = percutaneous transluminal coronary angioplasty.

USE OF CONTRAST IN THE CARDIAC CATHETERIZATION LABORATORY

Ideally, cardiac diagnosis and therapy would be performed noninvasively and without risk or discomfort to the patient. While less invasive procedures have proved helpful in the assessment of disorders of the heart and great vessels, delineation of the coronary tree by the direct instillation of radiographic contrast material remains the only available methodology for the detailed evaluation of coronary anatomy. Such angiography is also necessary for the safe and effective performance of catheter-based intervention. In 1990, approximately 1.3 million diagnostic and therapeutic procedures requiring coronary angiography will be performed and it is likely that there will be continued growth (albeit perhaps at a lessened pace) in the years to come. This increased usage is in part accounted for by the widening of indications to include older and sicker individuals and to the aggressive application of interventional techniques to more complex coronary disease. In addition, contrast exposure per case is increasing as the performance of multivessel angioplasty and the use of new tools such as atherectomy devices become more common. While the introduction of "noncontrast" imaging modalities, such as coronary angioscopy and intravascular ultrasound, offers the potential of reducing the need for contrast media, they are more invasive and will augment rather than replace the coronary angiogram.

TOXICITY OF CONTRAST

The toxicity of contrast media is clinically manifest by the occurrence of an adverse reaction. Most information available in this regard comes from large surveys comprised predominantly of intravenous studies. Untoward events have been reported to occur in from 5 to 10% of intravascular contrast studies with the suggestion that intravenous administration is associated with a higher incidence than is intraarterial administration.[6–12] Most reactions are classified as mild (requiring no treatment); however, it is estimated that about 500 contrast-related deaths occur in the U.S. each year with a mortality rate of approximately 1/40,000 examinations.[6,7] The pathophysiology of contrast reactions remains to be fully defined but many appear to be the result of nonantibody-related activation of vasoactive peptides and amines in predisposed individuals.[13,14] Contrast media have been shown to stimulate vascular endothelium with the resultant release of prostacyclin.[15] Pretesting with small doses of contrast media[12] and the measurement of precontrast blood levels of certain constituents (thromboxane B_2 and platelet factor)[16] may be predictive of such reactions. Pretreatment with steroids[17] and perhaps H1 and H2 blockers[18] may prevent such reactions. A role has been suggested for central nervous system mediation,[19] and some reactions attributed to contrast agents are due to procedural anxiety rather than the agent itself.[20]

Renal compromise associated with intravascular contrast administration is also complex in etiology.[21] Several risk factors have been identified,[22] although not all have been confirmed. The state of hydration appears to be of great import, and the recent increase in attention paid to this may account for a lessening in the incidence of acute renal failure.[23] On occasion, cholesterol embolization subsequent to aortic catheterization may be responsible wholly or in part for renal impairment.[24]

RISKS OF CORONARY ANGIOGRAPHY

The risks of coronary angiography result both from its invasive nature and the effects of the contrast media. The physical actions of gaining access to the arterial circulation, traversing the periphery and delivering the catheter to the selected site may result in vascular injury either directly or subsequent to embolization. Additionally, the catheter may significantly obstruct the coronary orifice, causing ischemia as well as limiting the washout of injected contrast.

Aside from the "allergic" reactions encountered with intravascular contrast in general, the intracoronary administration of contrast media may be associated with a variety of cardiac and systemic effects (Table I). Transient bradycardia and hypotension accompanied by marked electrocardiographic changes are seen almost universally with the HOM.[25] Bradycardia may be the result of sinus arrest or atrioventricular block and is usually responsive to having the patient cough or the administration of atropine. Rarely is cardiopulmonary resuscitation or pacing necessary. Both reflex and direct effects of contrast media have been implicated.[26–28] Ventricular

TABLE I Cardiac and Systemic Effects of Contrast Media

Hemodynamic
Systemic hypotension
Increased ventricular filling pressure
Electrophysiologic
Bradycardia
sinus arrest, AV block
Tachycardia
ventricular tachycardia/fibrillation
Discomfort
Pain
Nausea/vomiting
Renal compromise
"Allergic" adverse reactions
Hives
Itching
Rash
Bronchospasm

AV = atrioventricular.

tachyarrhythmias most often accompany long injections or injections through an "impacted" catheter. On occasion, this may occur at the end of a prolonged period of asystole, and pretreatment with atropine has been found beneficial.[29] While some episodes of ventricular tachyarrhythmia are self-limited, most require electrical conversion. Changes in the rate of upstroke and duration of the action potential have been noted after contrast injection,[30] and dispersion of ventricular refractoriness (seen clinically as prolongation of the Q-T interval)[31] may be important in the generation of ventricular arrhythmia.

Hypotension accompanying intracoronary contrast administration is due primarily to decreased contractility attributed to hyperosmolality, hypernatremia and calcium-binding additives.[32–34] Reflex peripheral vasodilation[35] may also play a role, as might direct peripheral vasodilation[36] and alterations of myocardial metabolism[37] when larger volumes of contrast media are delivered into the left ventricle or ascending aorta. In compromised patients (i.e., patients with severe heart failure, critical obstructive coronary disease or aortic stenosis) such transient hypotension may result in further left ventricular dysfunction, which in turn worsens the hypotension. In our experience, this cycle appears to be the most common cause of contrast-related death in coronary angiography. The increased ventricular end-diastolic pressure commonly encountered in patients undergoing coronary angiography and left ventriculography is due to changes in diastolic function,[38,39] ischemia[40] and the increased intravascular volume that accompanies administration of hypertonic contrast.[41] The degree of elevation in left ventricular end-diastolic pressure after coronary angiography has been suggested as a "stress test" of ventricular function.[42] The effects of contrast agents on left ventricular function may last for as long as an hour.[43]

While intracoronary contrast injection is usually painless, some discomfort may be experienced. On occasion patients with significant coronary disease develop typical angina pectoris accompanied by electrocardiographic changes and hypertension responsive to nitrate therapy. Peripheral arterial injections may elicit considerable discomfort attributed to intense vasodilatation. Such pain is often encountered during angiography of the internal mammary artery.[44] A sensation of intense heat is common after left ventriculography, while cough is noted during right ventricular and pulmonary angiography.[45,46]

The true incidence of contrast-induced adverse reactions complicating cardiac catheterization is not well established. While the relation between an untoward effect and intravenously administered contrast media is relatively easy to define, this is not the case with coronary angiography. Surveys of complications of coronary angiography may characterize only "allergic" events as due to contrast injection, while death and arrhythmia go without specific attribution. Thus, the 0.23% incidence of contrast reaction reported by the Society for Cardiac Angiography and Interventions[47] probably underestimates the true extent of contrast toxicity. An analysis of the major complications associated with cardiac catheterization and coronary angiography at the Johns Hopkins Hospital in the year before the introduction of LOM revealed 17 of 33 to be contrast related (Table II).

While major complications are not common, the incidence of minor contrast-related adverse reactions encountered during coronary angiography is extremely high. We noted some subjective or objective reaction to contrast media in 93% of 122 low-risk patients undergoing coronary angiography.[48] Most were mild and required little or no therapy; however, some health-care resource was consumed by 42% of those having an adverse reaction.[49]

THE IDEAL CONTRAST

The primary function of contrast is to attenuate x-radiation. Other effects are usually considered undesirable, although anticoagulant and vasodilating properties may at times be advantageous. The ideal contrast agent (Table III) would be nontoxic, provide excellent opacification, be easy to inject even through small lumened catheter systems, and be inexpensive. While such an agent does not currently exist, there are significant differences between the available families of contrast agents (Table IV). These may be put in perspective by examining their clinical implications.

OSMOLALITY

While the currently available contrast agents are all hyperosmolar compared to plasma, there is marked vari-

TABLE II Complications of Cardiac Catheterizations at the Johns Hopkins Hospital—1980–1981

Procedures	1,144
Significant complications (%)	33 (2.8)
Those related to contrast media (%)	17 (1.5)
Complications including	
Hypotension leading to death	3
Ventricular tachyarrhythmia	7
Renal failure	4*
Prolonged hypotension	3

* One of these patients also had cholesterol embolization and later died.

ation in degree. The traditional ionic HOM consist of a fully substituted triiodinated benzoate anion and a cation (e.g., sodium, meglumine), which in solution dissociates into 2 osmotically active particles, only 1 of which accounts for radiopacity. Thus, the ratio of iodine atoms to osmotically active particles is 3 to 2 or 1.5. The newer LOM achieve a lessened osmolality by either increasing the number of iodine atoms/osmotically active particle or decreasing the number of osmotically active particles/iodine atom. The ionic dimer hexabrix (6 iodine atoms/2 active particles) is an example of the former, while the latter is exemplified by the nonionic agents (3 iodine atoms for each particle). In either case, there is a resultant ratio 3 compound, which reduces the osmolality of the new agents to about half that of the traditional HOM. It should be emphasized that despite this lessened osmolality, the new agents still have over twice the tonicity of plasma. Recently, nonionic dimers with a ratio of 6 iodine atoms/active particle have been introduced. These agents offer the possibility of isoosmotic contrast, which may be associated with even lessened toxicity.

The hyperosmolality of traditional HOM has been implicated as contributing to many of the untoward effects of contrast media, including the release of vasoactive substances.[34,50,51] Several large-scale (but nonrandomized) studies[52–54] comparing the intravenous administration of HOM and nonionic contrast media conclude that the latter result in less risk of mild, moderate and severe untoward events. Furthermore, while one may, on the basis of a number of discriminators, stratify patients into high- and low-risk groups for experiencing a contrast reaction, this is not as predictive as is the type of contrast received. The incidence of a significant untoward event occurring in a low-risk patient receiving HOM is higher than that of a high-risk patient receiving a nonionic agent.[53] LOM appear to decrease the risk of contrast reaction in previous contrast reactors.[55]

When compared to HOM in coronary angiography, there is less perturbation of the electrocardiogram (e.g., increased R-R and Q-T intervals, change in T-wave amplitude)[56–58] and a decreased incidence of significant bradycardia and ventricular tachyarrhythmias[59] associated with LOM. The high osmolality agents are not only more frequently associated with significant hypotension but the degree of blood pressure depression is more than that incurred with LOM.[57,58,60–62] Changes in left ventricular filling pressure,[42,60] diastolic function[38] and cardiac metabolism[63] are more prominent with HOM and there is a greater expansion of the circulating plasma volume.[41]

TABLE III Properties of an Ideal Contrast Agent

- Nontoxic
  - Isosmolality
  - Nonionic
  - ? Sodium
  - Inert additives
  - Noncalcium binding
- Low viscosity (room temperature)
- Optimal iodine content
- ? anticoagulant
- Inexpensive

The traditional high osmolality agents are associated with more side effects, including hives, nausea/vomiting and discomfort.[60] Cough associated with pulmonary angiography[45,46] and pain associated with peripheral arterial injection occur less often with LOM. It has been suggested that the high-risk cardiac patient benefits from LOM,[64] although there are a paucity of comparative data due to reticence to randomize such patients. Retrospective analysis suggests that there is less morbidity and mortality with LOM.[65] The hope was that LOM also would reduce the incidence of renal compromise; however, there is little clinical evidence that this is so.[66,67]

IONICITY

Among LOM, the nonionic agents appear to be better tolerated than the ionic dimers despite the lower osmolality of the latter. There is a lessened incidence of adverse reactions (nausea/vomiting, chest pain and allergic manifestations)[68,69] and there are fewer electrocardiographic changes.[70] Animal studies suggest that there are hemodynamic advantages of the nonionic agents over ionic LOM both in the normal and in the ischemic state (Fig. 2).[71]

TABLE IV Contrast Media

Brand Name	Compound	Osmolality mosm/kg H_2O	Viscosity (CP) Rm Temp	37	Iodine mg/ml	Sodium+ (mEq/liter)	LD_{50} Mouse (g Iodine/kg)	Additives
Hypaque, 370	Sodium-meglumine diatrizoate	1,690	13.3	9.0	370	160	5.3–8.0	Calcium disodium EDTA
Renografin-76	Sodium-meglumine diatrizoate	1,940	10.0	8.4	370	190	5.3–8.0	Sodium citrate, disodium EDTA
Hexabrix	Sodium-meglumine ioxaglate	600	15.7	7.5	320	150	11.2	Calcium disodium EDTA
Omnipaque	Iohexol	844	20.4	10.4	350	5	24.2	Tromethamine calcium disodium EDTA
Isovue	Iopamidol	796	20.7	9.4	370	2	21.8	Tromethamine calcium disodium EDTA
Optiray	Ioversol	702	9.9	5.8	320	2	17	Tromethamine calcium disodium EDTA

EDTA = diaminetetraacetic acid; I = iodine; LD_{50} = lethal dose in 50% of injected animals; Rm Temp = room temperature.

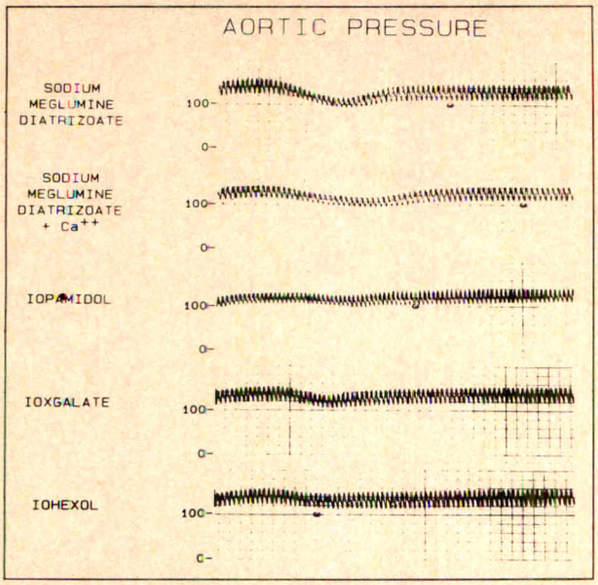


FIGURE 2. Effect of left coronary injection of a variety of contrast media in a canine model. Note that hypotensive effect of ioxaglate is midway between that of traditional hypertonic media and the nonionic agents. Also, the addition of calcium in the diatrizoate compound does not completely reverse its hemodynamic effect. Ca^{++} = calcium.

Controversy currently exists as to whether there is an increased propensity for thromboembolic events associated with the use of nonionic contrast. This possible relation was highlighted by the report of Grollman et al[72] of 3 such complications occurring in 1,380 patients undergoing coronary angiography with a nonionic contrast. It was suggested that these patients may have been inadequately heparinized and that the level of anticoagulation may be more important in patients being studied with nonionic contrast. Further reports of "clots" forming in syringes when blood is exposed to nonionic contrast agents raised the possibility that these agents may be procoagulant. It has subsequently been shown that benign red blood cell aggregates form in nonionic contrast media, are readily dispersed on agitation, and do not have clinical sequelae.[73] As might be expected, nonionic agents cause less perturbation of the coagulation system than do ionic contrast media; however, they do exhibit some anticoagulant activity.[74–77] It has recently been suggested that thrombin may be generated by exposure of blood to nonionic contrast media without the formation of clot because the contrast media prevent fibrin polymerization.[78] Heparinization prevents thrombus formation.[79] While the clinical significance of this remains to be defined, recent analysis of over 8,000 patients undergoing coronary angiography with nonionic agents revealed an incidence of thromboembolic events of 0.18% with no difference regardless of whether systemic anticoagulation was used.[80] This compares favorably to the experience with ionic agents.

Coronary angioplasty may be complicated by thrombotic occlusion of the dilated segment. A nonrandomized study suggested that thrombus forms more frequently when nonionic contrast media are used.[81] A larger scale, randomized, controlled comparison of nonionic and ionic contrast failed to reveal a difference in acute occlusion, myocardial infarction or the need for urgent surgery. However, it did show a significantly lessened incidence of ventricular tachycardia and fibrillation in the nonionic cohort.[82]

It would appear that whatever contrast agent is used there is a small but finite risk of thromboembolism. There is no substitute for meticulous angiographic technique, which in the case of coronary angiography seems more important than systemic anticoagulation. Angioplasty presents a complex problem. The role of adequate heparinization in these cases is commonly accepted; and it is thus unlikely that nonionic contrast media offer any increase in risk of acute occlusion while probably reducing the overall incidence of untoward events.

SODIUM CONTENT

The importance of sodium content in ionic contrast was exemplified by the increased occurrence of malignant ventricular arrhythmias when the sodium contraction of Renografin-76 was decreased from 190 to 40 mEq/liter.[83] The presence of excessive sodium, however, has disadvantages, the most obvious being a decrease in myocardial contractility.[33] Nonionic agents have almost no sodium yet have been associated with a very low incidence of ventricular dysrhythmia. Two generally accepted experimental models exist to test for the propensity of developing ventricular dysrhythmia. One uses a catheter impacted in the right coronary artery and relatively long injections of contrast media to provoke spontaneous ventricular tachycardia or fibrillation. This model has shown a benefit of the presence of sodium even with nonionic contrast media,[84,85] although hyperosmolality may be more critical than the lack of sodium.[86] The other model that accompanies bolus contrast injections with programmed ventricular extrastimuli has shown nonionic contrast media to be less arrhythmogenic than either HOM or ionic LOM.[87] This model fails to show a benefit of sodium addition to nonionic contrast media.[88] It is not clear which of these methods best duplicates the clinical situation. While ventricular tachycardia/fibrillation often occurs after a long injection, especially if from an impacted right coronary catheter, nonionic contrast media are associated with a very low incidence of these events. Whether this incidence would be even lower with the addition of sodium remains to be proven.

ADDITIVES

The use of nonradiopaque substances to stabilize and buffer contrast solutions may produce undesirable effects. There is a greater prolongation of the electrocardiographic Q-T interval,[89] a higher incidence of ventricular fibrillation[90] and a more marked negative inotropic effect encountered when Renografin-76 is used compared to similar HOM (Hypaque and Angiovist).[91] The etiology of these differences is the increased calcium binding exhibited by the additives to Renografin-76 (sodium citrate and sodium ethylenediaminetetraacetic acid [EDTA]) compared to that of the other HOM (calcium disodium

EGTA). It should be noted that many of the studies comparing HOM and LOM use Renografin-76 as the HOM comparator. The additional toxicity associated with the additives to this agent tends to magnify the difference between the 2 classes of contrast.

IODINE CONTENT

As previously mentioned, the radiopacity of contrast media is due to iodine: the greater the concentration of iodine, the more radiopaque the contrast. Traditionally, coronary angiography and left ventriculography have been performed with contrast media containing 370 mg/ml of iodine. This has provided excellent imaging and may be considered the standard. Since the viscosity of contrast media is related to the iodine concentration, many of the LOM are formulated with less iodine to maintain acceptable viscosity. Randomized studies visually comparing the quality of angiograms have not, for the most part, revealed a detectable difference between the HOM containing 370 mg/ml of iodine and the LOM containing 320 or more mg iodine/ml. There has been the suggestion in children, however, that clinically superior imaging was achieved with contrast media containing 370 mg iodine/ml compared to contrast media having 320 mg iodine/ml.[70]

COST

The differential in cost between LOM and HOM in the U.S. (15 to 20 times) exceeds that in other countries (5 to 10 times) because of the higher cost of LOM and lower cost of HOM in the U.S. For a cardiac catheterization laboratory performing 1,000 cases/year and using 250 ml of contrast media/case, the expenditures for contrast media would increase from $17,500 to $250,000 if LOM replaced HOM. It has been suggested that a high-volume radiology department's budget for contrast media would increase from $200,000 to $2.6 million by switching completely from HOM to LOM.[92]

One justification for the use of the more expensive agents would be if the decreased incidence of untoward effects resulting from their use conserved resources that would otherwise be expended. A detailed analysis of total cost incurred by untoward reactions in a group of low-risk patients undergoing cardiac catheterization with HOM revealed that even if all untoward effects were abolished with LOM, only about 10% of its additional cost would be recouped by the hospital.[49] There are of course benefits of LOM that are not easily defined in terms of economics. These include improved patient comfort, the ability to perform more complete studies in sicker patients and a greater sense of security on the part of the physician. Even so, the ethical and financial implications of LOM continue to be debated.[92–95]

An economically responsible stance might be to limit the use of LOM to those patients at increased risk of complication. While one may prospectively identify such patients with a reasonable degree of certainty, experience with intravenous contrast media indicates that low-risk patients given HOM are at higher risk of a reaction than high-risk patients receiving LOM. If there is to be limited use of LOM, an accepted guideline may be more helpful in ensuring that all high-risk patients get LOM than excluding those at low risk (Table V).

TABLE V Guidelines for Use of LOM

Hemodynamic instability
Pressor dependent
Intraaortic balloon
Systolic BP <90 mm Hg
Significant ventricular dysfunction
Electrophysiologic instability
Marked pulmonary hypertension (systolic BP <60 mm Hg)
Severe valvular disease
Severe coronary artery disease
PTCA (?)
Dehydration
Previous contrast allergy
Other allergic history (?)
Dysproteinemia
Hemoglobinopathy
Extreme patient apprehension
Need for painful angiography (e.g., IMA)
Hyperosmolar state
Renal compromise (?)
Large anticipated contrast dose

BP = blood pressure; IMA = internal mammary artery; LOM = low osmolality media; PTCA = percutaneous transluminal coronary angioplasty.

SUMMARY

The current generation of low osmolality contrast material represents but a step in the continued evolution of vascular imaging. These agents are better tolerated than the traditional HOM and offer advantages to the cardiac angiographer. The nonionic agents produce the least physiologic perturbation, and while controversy continues over the relation of these agents to thromboembolism, increasing evidence suggests that the incidence of such events is no different from that encountered with ionic contrast. Nonionic agents are associated with fewer adverse reactions than the low osmolality ionic agents and would appear to be the contrast agents of choice.

The cost of all LOM is about the same, and under the conditions of the current reimbursement system, stress the budgets of most institutions. Approaches to this problem include: (1) limiting the use of LOM to those patients thought to be at increased risk of a complication[96]; (2) attention to methods of conservation of contrast media,[97] including the possibility of a multiple dosing system; (3) competitive contracting; and (4) petitioning for universal third party reimbursement.

Presently the consensus is that LOM is preferred for coronary angiography and most patients undergoing this procedure currently receive such an agent. Thus, a new community standard is being established that may present a complex problem for hospitals excluding their use solely on an economic basis.[98] It is extremely difficult to justify the use of HOM in high-risk patients, although there are still some proponents of universal use of these agents.[99] It would be interesting to consider whether, had LOM been introduced first, there would be any enthusi-

asm for the use of the cheaper but less well tolerated HOM.

The debate over cost versus benefit is likely to continue as newer, potentially better-tolerated isosmotic agents are introduced, which may be yet more expensive. While being sensitive to economic issues, the physician's primary obligation is to the patient. The physician now has a variety of contrast materials from which to choose and thus a responsibility to select the most appropriate agent for each patient.

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Contrast Media Safety: What Do We Know and How Do We Know It?

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Use of an intravenous injection of a water-soluble iodine compound (sodium iodide) for visualizing the urinary tract was first described by Osborne in 1923. However, sodium iodide was accompanied by a high incidence of side effects and the image quality was not good.

As newer, improved contrast agents were introduced, a number of investigators reported on the incidence of death and side effects incurred by their use. In 1975, the first large-scale, multicenter, prospective study on the incidence of fatal and nonfatal reactions was reported by Shehadi. In this series, the overall incidence of adverse reactions was 5.65%, of which 3.77% were mild, 1.77% were moderate, 0.02% were severe, and 0.0007% were fatal. Shehadi also noted that a history of allergy doubled the risk of adverse reaction and a history of a previous adverse reaction to contrast material trebled the risk; also, the risk of a reaction to an intraarterial injection was half that of the risk associated with an intravenous injection.

With the introduction of low osmolar nonionic agents, other large-scale studies were performed because these agents appeared to cause significantly fewer adverse reactions. However, they were from 10 to 15 times more expensive than their predecessors.

In 1987, Lasser reported on the increased safety of ionic agents when patients were pretreated with steroids. Palmer in Australia and Katayama in Japan collected 120,000 and 335,000 patients, respectively, and compared the incidence of adverse reactions of the ionic versus the nonionic agents. Wolf recently reported a study that included a direct comparison of ionic agents with pretreatment with steroids versus nonionic agents.

The Katayama study is the most powerful statistically, and this, supported by both Wolf's study and Palmer's study, indicates that the single most important risk factor is the type of contrast agent used, with a nonionic agent having between 14 and 17% of the incidence of adverse reactions, and between 4 and 17% of the incidence of severe adverse reactions.

These studies have resolved the issue of safety of the ionic agents versus the nonionic agents. The safety of ionic agents with steroid pretreatment remains to be established. Choice of a contrast agent now rests on considerations of cost, ethics and liability.

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In 1923, Osborne et al[1] of the Mayo Clinic reported on the first in vivo use of an intravenous injection of a water-soluble iodine compound (sodium iodide) for visualizing the urinary tract. In 1927, Moniz[2] used sodium iodide for carotid angiography. Sodium iodide produced a large number of adverse reactions, many of which were severe. Over the next 2 decades, extensive industrial research yielded less toxic contrast agents with better visualization of the organs being studied. In the early 1950s the diatrizoates were introduced, and in the 1960s iothalamate was introduced. These latter 2 compounds were much better tolerated and were relatively safe and efficacious.

In 1942, Pendergrass et al[3] reported the results of an informal survey, which showed an incidence of 39 deaths/million urograms. In 1955, a follow-up survey by Pendergrass et al[4] yielded an incidence of 6.5 deaths/million urograms. In 1973, Whitten et al[5] reported on 32,964 outpatients undergoing excretory urography using diatrizoate contrast media. The overall incidence of adverse reactions was 6.8%, with severe reactions representing 0.09%. There was 1 death in this series.

In 1975, Shehadi[6] reported on a prospective survey in 30 teaching hospitals in the United States, Canada, Europe and Australia consisting of 112,003 patients. The patients had undergone intravenous and intraarterial injections of ionic contrast media. There was an overall incidence of adverse reactions of 5.65%, of which 0.02% were severe. Eight fatalities were reported.

In 1980, Shehadi and Toniolo[7] reported on a prospective survey of 302,083 patients examined with intravascular contrast media. This was an international study involving the U.S., Canada, Australia and several European countries. The overall incidence of adverse reactions was 4.7% with 0.072% being severe, and there were 18 fatalities. The risk of adverse reactions doubled with a history of allergy. With a history of a previous adverse reaction to contrast material, the risk trebled. An intraarterial injection resulted in half the number of adverse reactions as an intravenous injection.

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This modern era of ionic agents was characterized by a relatively low incidence of adverse reactions and the drugs were regarded as safe and effective. However, the persistence of occasional severe reactions (including death) resulting from strictly diagnostic procedures spurred the search for an even safer agent.

NONIONICS

Almén[8,9] theorized and eventually developed the first clinically used nonionic contrast agent, metrizamide, in the 1970s. This agent was primarily used for myelography, but the experience with intravascular use quickly demonstrated that it produced less discomfort and seemed to be safer than the ionic class of agents. Metrizamide, because of its instability, was lyophilized and had to be mixed into solution before its use. The late 1970s saw the introduction of stable nonionic contrast agents for intravascular use. Schrott et al[10] in 1986 reported on 50,666 consecutive patients undergoing intravenous urography with a nonionic agent in a prospective multicenter study. The overall incidence of reactions was 2%, while the incidence of severe reactions was 0.01%. The patients were divided into 2 groups. Those without risk factors had an overall incidence of 1.3% and a severe reaction rate of 0.004%. In the patients with risk factors, the overall incidence was 2.7% and the rate for severe reactions was 0.02%. This series demonstrated that the high-risk patients were at 2 times the risk for reactions overall, and at 5 times the risk for severe reactions when using nonionic contrast agents.

COMPARISON OF IONIC AND NONIONIC AGENTS

There are 2 very large studies comparing the incidence of adverse reactions in patients receiving either ionic or nonionic contrast media. Palmer[11] in Australia and Katayama[12] in Japan collected 109,546 and 337,647 contrast studies in a prospective fashion, respectively. Palmer found the incidence of severe adverse reactions in the ionic group to be 0.09% and in the nonionic group, 0.02%. In a more detailed and controlled study, Katayama[12] reported the incidence of severe adverse reactions in the ionic group to be 0.25% while the severe adverse reactions in the nonionic group was 0.04%.

PRETREATMENT WITH STEROIDS

In 1987, Lasser et al[13] reported on the use of pretreatment with steroids in patients receiving ionic contrast media in a prospective, randomized, double-blind study. The incidence of overall reactions with steroid pretreatment was 6.4% and of severe reactions (which he called class III reactions) was 0.2%. He compared these results with those reported by Schrott et al[10] and concluded that pretreatment with steroids and the use of ionic agents offered the same order of safety as did the nonionic agents.

Because Lasser's class III reactions did not match Katayama's definition of severe reactions, Lasser reanalyzed his data using Katayama's definitions (personal communication) and reported an incidence of severe reactions in the steroid plus ionic category of 0.08% as compared to Katayama's 0.04% in patients receiving nonionic agents.

In 1989, Wolf et al[14] reported on a direct comparison of patients receiving ionic agents alone, pretreatment with steroids plus ionic agents and a nonionic agent. In a series of 15,668 patients, little difference was noted between the group receiving the ionic agent alone and the group receiving pretreatment with steroids followed by the ionic agents. There was a sevenfold decrease in overall adverse reactions in the patients receiving the nonionic agent and a 25-fold decrease in severe adverse reactions in patients receiving the nonionic agent.

DISCUSSION

Multiple studies from around the world have demonstrated an improved safety profile of the nonionics as compared to the ionic contrast agents, with the safety factor for overall reactions ranging from 2:1 to 7:1 and the safety factor for severe reactions ranging from 4:1 to greater than 25:1, all of these in favor of the nonionic agents.

None of the aforementioned studies is without weaknesses. Only 1 was randomized and double-blinded (Lasser et al[13]). However, Lasser et al did not include the use of nonionic contrast agents in their study and, because the study was relatively small, the confidence limits of the statistical data are very broad.

In the study of Wolf et al,[14] which directly compared an ionic agent alone, pretreatment with steroids plus an ionic agent, and a nonionic agent, the patients were not randomized and the study was not blinded. It was a crossover study and the individual hospitals participating in the study were blinded and randomized. Because of the difficulty with getting compliance for the patients scheduled to receive pretreatment with steroids plus ionic contrast agents, this group is small, again yielding broad confidence limits for the comparison of this group with the group receiving ionic agents alone and the group receiving nonionic agents.

The study of Palmer[11] lacked details necessary for analysis and comparison of the various subgroups of patients within the 2 broad categories of ionic and nonionic agents. Further, there is no available information on the number of patients whose results were unreported or the reasons for their not being reported.

Because of the large size of the study of Katayama,[12] it is statistically powerful. A retrospective audit of this study estimated that between 59 and 82% of the patients scheduled for the study were, in fact, enrolled. Thus, there is the potential for bias. However, an analysis of the details of the 2 arms of the trial, and specifically the distribution of the various characteristics analyzed in this study, fails to demonstrate any significant trend indicative of bias. Children (under 30 kg) were preferentially given the nonionic contrast media. Similarly, patients undergoing intravenous digital subtraction angiography were more frequently given nonionic contrast media.

Both of these subsets represent very small components of the study and it is unlikely that either of these factors significantly influenced the results. In all of the other important categories, there was good balance between the group of patients receiving ionic contrast agents and those receiving nonionic contrast agents. Thus,there is no evidence of systematic bias in any of the other subgroups analyzed.

All of the studies directly comparing adverse reactions and severe adverse reactions in the ionic and nonionic groups demonstrate that the single largest risk factor for developing an adverse reaction is the use of ionic contrast agents. Other important risk factors include a previous reaction to contrast agents, a history of allergy or asthma, and a history of cardiac disease. None of these is as great as the use of an ionic contrast agent.

IONIC AGENTS VERSUS NONIONIC AGENTS: WHICH TO CHOOSE?

This question leads to the dilemma we currently face. The newer agents are 10 to 15 times more expensive. The greatest risk to the patient is the use of the ionic agents. Yet, severe reactions and death from the ionic agents are uncommon. Before the introduction of nonionic agents, approximately 10 million contrast examinations were performed annually in the U.S. The cost of contrast material for these studies was $100 million/year. The cost for performing the same number of studies using only nonionic agents would have been approximately $1 billion/year.[15] Are there more important ways that these additional dollars could be spent? What is the physician's responsibility to the individual patient referred for a study and how does that compare with the physician's responsibility to the cost of delivery of medical care in the U.S.? What are the ethical duties and legal liabilities associated with the use of an ionic contrast agent in a patient with no other identifiable risk factors? Certainly, if the cost were the same or if the new agents were only 2 or perhaps 3 times more expensive, virtually everyone agrees that there would be no reason to use ionic agents.

If the figures from the Katayama study are transferred to the U.S., we would expect 22,000 severe adverse reactions each year if only ionic agents were used. If everyone received nonionic agents, there would be an estimated 4,000 severe adverse reactions per year. What is an appropriate expenditure of dollars to prevent 18,000 severe reactions per year? Although Katayama reported only 1 death in each arm of the study, it is stated that no causal relation to the contrast media could be established. Of the 18,000 severe reactions that are potentially avoidable every year in the U.S., some percentage are going to have a fatal outcome. What is an appropriate expenditure to avoid these deaths?

The answers to these questions require input from physicians, hospital management, ethicists, attorneys, third-party payors and the government.

In conclusion, despite the lack of a "perfect study," the data overwhelmingly demonstrate the relative safety of the nonionic agents when compared to the ionic agents. The safety of premedication with steroids plus ionic agents is still unanswered. The issue comes down to cost, ethics and liability.

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The Cardiac Catheterization Laboratory—1990

Carl J. Pepine, MD

Over the past several decades, there has been an evolution and proliferation of catheterization laboratories. During the latter half of the 1980s, these changes have resulted from the development of a number of catheter-based therapeutic techniques.

In general, it would seem reasonable to predict that the 1990s will continue to show expansion of laboratory services in both traditional hospital and nontraditional settings. In the latter, the free-standing laboratories will probably grow substantially. The types of patients studied in this new era will continue to be largely those with suspected or known coronary artery disease.

The most dramatic changes in laboratory configuration will be in the image system. High-definition systems will become the standard. Images will be recorded direct to solid-state memory using fluoroscopic techniques. Resolution will be increased at reduced noise and enhanced contrast. Higher resolution video monitors and video recorders will be the cornerstones of the laboratory. The image information for an entire day's work will be stored first on a digital tape system, probably a rapidly accessed reel system, and by the late 1990s in solid-state memory. Individual case data will then be copied to smaller cassettes for patient reports. An entirely digital system will provide rapid electronic acquisition, processing, storage and transmission of information. In addition, physicians will be able to call up previous studies that have been copied to this format for storage. Storage space will be reduced considerably. Access of information will be relatively rapid compared with cine equipment.

Other new procedures that appear to have some application in many catheterization laboratories by the mid-1990s include procedures to image the vascular wall at its surface and in cross-section: microangioscopy, intravascular echocardiography and transesophageal echocardiography also will spur development of new contrast agents. These procedures will be used for both diagnostic and therapeutic studies. Quantification of the significance of coronary artery stenosis will come in the form of refinements of digital technique. Digital calipers will be commonplace and used to measure minimal area rapidly as the procedure is done. Likewise, reactive hyperemia will also be determined by digital technology. In addition, there is a need to evaluate the coronary microvasculature. Here, digital techniques will probably be used and it may also be possible to use miniaturized Doppler velocity techniques.

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There has been an evolution in cardiac catheterization laboratories. Over the past decade the traditional diagnostic laboratory has proliferated and appears to be changing its form and purpose.[1] Also, the development and widespread acceptance of percutaneous transluminal coronary angioplasty (PTCA) and a number of newer techniques and devices have resulted in the construction of laboratories dedicated to therapy. What follows is a philosophical look and some predictions for catheterization laboratories in the next decade. The comments are my thoughts and should not be construed to reflect those of any of the committees on which I now serve.

WHERE WILL THESE CATHETERIZATION LABORATORIES BE LOCATED?

It is convenient to think of this question in terms of the traditional cardiac catheterization laboratory, which flourished in a large medical center closely allied to a teaching/research environment and evolved from a diagnostic laboratory to a therapeutic laboratory. In the 1990s, the majority of cardiac catheterization laboratories will retain that traditional environment. Over the past 5 to 7 years, there has been a tremendous proliferation of nontraditional cardiac catheterization laboratories. These laboratories have been called "free-standing," mobile or modular. Free-standing laboratories may be defined as such because they are not physically connected to a hospital; they may be as close as next door, across the street, several miles away or even actually quite a distance from a hospital. Mobile cardiac catheterization laboratories are unique because they are transportable by some means. Modular laboratories are constructed by multiple mobile laboratories joined together by a coupling device. This type of nontraditional laboratory growth has been permitted largely because of the government's nonrestrictive attitude over the past decade toward the development of laboratories. It has been my view that this is not optimal for quality or cost of the general practice of cardiac catheterization. One recent large study by the Rand Corporation reached the conclusion that the proliferation of other laboratory services in an unrestricted environment actually contributed to increasing the cost of catheterization procedures by increasing the total number of cases. I

think that only 1 of these types of laboratories will exist in any great number in the 1990s—the free-standing laboratory in very close proximity to a large medical center. Mobile or modular laboratories will be used as temporary structures while existing laboratories are refitting obsolete equipment or while they are expanding or developing services, but I do not think that mobile laboratories will constitute an important part of our practice in the coming decade.

WHERE WILL THE PATIENTS COME FROM?

In many hospitals right now, the majority of patients are ambulatory and spend no overnight period in the hospital related to catheterization. This practice will probably increase in most hospitals over the next decade. The hospitalized patients will comprise a declining proportion of the total catheterization laboratory volume and will be made up largely of high-risk or unstable patients.

WHAT TYPES OF SERVICE?

It's convenient to think of catheterization laboratories as either all purpose laboratories providing a variety of services or very specialized laboratories with focused activities. The latter may be either diagnostic, therapeutic, electrophysiologic, pediatric, biopsy or other. I think most of the laboratories to evolve in the 1990s will be specialized. Therapeutic laboratories will expand, as will electrophysiologic laboratories. I do not think that laboratories for the pediatric sector will increase, because of the relatively stable patient volume and the specialized care they require. There will probably be, however, an increasing number of catheter-based therapeutic procedures performed on these patients.

It is necessary to address whether therapeutic laboratories will have the ability to perform interventional cardiac catheterization procedures in an environment unsupported by on site cardiac surgery. To my knowledge, the first report of an attempt to use coronary angioplasty in a noncardiac surgical hospital comes from Northern Ireland,[2] where 540 patients underwent PTCA in a hospital 2.4 km away from its affiliated hospital with cardiac surgery support. Both hospitals were located on major highways and ambulance service provided transport within 15 to 20 minutes in all types of traffic conditions. The success rate for PTCA was 82%, probably similar to current angioplasty rates including a wide variety of patients. The acute occlusion rate was 6.5%, which was slightly higher than a level I consider desirable. A successful repeat PTCA was performed in 2% of patients with acute reocclusion. Interestingly, another 2% of patients with acute reocclusions were "medically treated," and an additional 2% were referred for "urgent" coronary bypass surgery. The time of delay between recognition of the occlusion and the institution of cardiopulmonary bypass averaged 268 minutes, suggesting a change in the definition of "emergency" to "urgent." The Irish investigators felt that the 2% rate of those going on to coronary bypass surgery was good (in the United States, only 2 to 3% of patients who undergo elective angioplasty go on to emergency bypass surgery, but this includes almost all patients. There were no deaths in the group that underwent urgent bypass. In this study, the death rate from PTCA was 1%. At least 3 of the 5 deaths were related to the acute occlusion, according to the investigators. This outcome would probably be unacceptable in the U.S., where the real test of this approach and outcome would be in the courts. Outcomes such as those reported in the Irish study will support the development of the traditional variety of cardiac catheterization laboratories rather than the growth of interventional procedures performed in noncardiac surgery environments. There is the possibility that other technologic advances, such as stenting or perfusion catheters, may allow for interventional therapy to be performed in the latter scenario.

WHAT TYPE OF EQUIPMENT WILL BE USED?

The x-ray systems will undergo extensive modification in the 1990s. We will probably have a similar number of biplane and monoplane facilities. There will be more miniaturization of the x-ray support equipment and the actual x-ray equipment itself as we move to totally filmless laboratories. We will return to some type of rotational table that will provide additional ability to view the proximal left anterior descending artery and make other fine modifications of angulation even when one has a biplane system. More laboratories will begin to use the new carbon fiber tables. The new video systems with high-definition monitors will be a welcome addition. Industry is now using these monitors with spectacular imaging characteristics. Additional modifications will occur in fluoroscopy, in terms of progressive scanning and circuitry modifications, that will both enhance the ability to resolve smaller structures and limit radiation. There will be a move toward larger image tube field sizes as cardiologists become more involved in evaluating and treating the peripheral circulation. A secondary need for the larger field size image intensifiers is the increasing number of patients that are being evaluated for heart failure. While this number is related in part to cardiac transplant programs, around the country there are larger numbers of elderly people being evaluated for heart failure than in the past. To visualize these large hearts, we are going to need larger field sizes.

The "filmless laboratory" will be the most exciting.[3] I envision that within 5 years we will have no need for cinefilm acquisition. Elimination of film should remove a costly equipment component, as well as the need for processors and projectors, and decrease the production of toxic waste water. Total electronic acquisition of the image will permit not only digital processing but the ability to store the image information in electronic media, retrieve it very quickly, and allow comparison with previous studies. In addition, electronic acquisition of data will allow side-by-side as well as superimposition comparison of injections from the same study, manipulation of images, and, probably most important, the transmission of the material from hospital to hospital and within the same hospital.

WHAT TYPE OF CONTRAST AGENT?

The benefits of nonionic versus ionic contrast media are still being debated, and new contrast agents will con-

tinue to be evaluated. Because of their safety, I use the nonionic agents routinely in all cases. Endothelial binding contrast agents are under development. With these agents, 1 injection is sufficient for the acquisition of multiple pictures from several views, and to image continuously during an interventional procedure.

Among new imaging agents, injection of carbon dioxide into the descending aorta provides excellent contrast on a digital angiogram and a very interesting image of the blood vessel surface composed of carbon dioxide and lumen wall. This surface image is different from that created by conventional radiographic contrast. By subtracting the 2 images, it may be possible to obtain a border image that contains additional information. In addition, contrast agents will be needed for the new imaging techniques outlined below. This technology could tell us more about the surface of plaques.

WHAT TYPE OF NEW IMAGING TECHNOLOGY?

Microangiography and intravascular ultrasound: With increasing interest in the vascular wall, particularly the surface of the endothelium, catheterization laboratories will begin to add some techniques to image the endothelial surface. I have been particularly impressed with results from the use of microangioscopy and ultrasound.

There is an increasing need to provide tomographic views of both the vessel wall and its lumen as we learn more about the biology of plaque. Intravascular ultrasound is well suited for this purpose and has provided excellent details of the results of interventions. Intimal fractures or fissures, dissections and the degree of stenosis are visualized and quantified. Catheters are being miniaturized and the detail of the images is getting better. In the coronary circulation, we are interested in mural thrombus that adheres to plaques. Many of these plaque-like vegetations are not detected by conventional high-resolution coronary angiography. The ability to visualize a thrombus adherent to the endothelial surface is provided by intravascular ultrasound, as well as microangioscopy. As these devices improve, we are likely to be routinely inserting "scopes" into at least the proximal and mid-coronary arteries of many patients.

The potential applications of ultrasound are exciting because this technology allows visualization of layers of the coronary artery wall. Three-dimensional reconstruction can be created from multiple images as the probe is moved. This type of study will be added to conventional coronary angiography to provide data about the arterial wall, plaque compositions, thrombus and other structures. We also will need new technology to assess the microvasculature because of the large number of patients we are seeing with relatively normal-appearing large-vessel coronary anatomy and signs of ischemia. Refinement of digital angiographic procedures to assess the microvasculature will evolve. Also, intracoronary Doppler flow probes have been in experimental use for years and these probes can now be miniaturized and become part of a coronary angiographic or ultrasound imaging catheter. This will permit assessment of anatomic as well as physiologic parameters. The need to quantify coronary artery stenoses will probably increase until we finally recognize that the intravascular luminogram is very limited, even with a quantification technique. Nonetheless, we will see routine application of simple tools such as the digital calipers to allow assessment of the stenosis measurements on line.

Transesophageal echocardiography: Transesophageal echocardiography provides superior images of the left atrium, mitral valve and proximal coronary arteries. It is useful in the catheterization laboratory to guide transseptal catheterization and evaluate possible thrombi in the left atrial appendage. Also, transesophageal echocardiography has been used to visualize the proximal left main coronary artery and assess coronary flow reserve during intracoronary injection of ultrasonic contrast. Use of transesophageal echocardiography could improve a number of catheter-related procedures. I look for this technique to be used more frequently in the catheterization laboratory.

Tomographic reconstruction: New technologies in the catheterization laboratories will involve new methods to improve spacial resolution and quantification. Cine computed tomography may receive a resurgence of interest, but 3-dimensional reconstruction from conventional digital biplane fluoroscopy is very promising. Reconstruction of both the heart and coronary arteries can be done line-by-line using algebraic reconstruction techniques. A 3-dimensional volume is created, which superimposes the left ventricular cavity, wall and coronary arteries. Tomographic cross-sections of the cardiac chambers and coronary arteries are then generated and volumetric reprojection and surface rendering result in 3-dimensional visualization. This technique should improve quantification of coronary arteries, ventricular pathology and the anatomic relations of the two.

REGULATORY ISSUES

Regulation is an area of great importance. We are on the brink of a tremendous increase in regulation, not only of the catheterization laboratory itself but also of those who work there. These problems can be divided into 3 areas: quality assurance, environmental pollution and reimbursement.

There is increasing demand for quality assurance, and we will see a proliferation in quality assurance procedures. We will see enforcement of some absolute volume indicators for both laboratories and operators. This will limit some of the extremely low volume laboratories but there is fear that such enforcement will serve to drive the marginal volume laboratories and operators to do more, and perhaps unnecessary, procedures. For this reason, the quality assurance procedures will be very extensive. A potential concern is the operators who keep their own quality assurance records, which is standard practice in many laboratories. This practice will become obsolete as quality assurance practices will be mandated to be enforced by unbiased individuals. In the recent past, a minimum volume number for operators was suggested to maintain a level of competence. These numbers resulted from estimates required for appropriate training al-

though there is no documentation to support any minimum volume number.

In the 1990s, some ceilings will also be placed on the maximum volume an operator can handle effectively. There are now no guidelines relative to a ceiling volume, but guidelines are needed. The operator of a very large volume coronary angiography/angioplasty practice becomes limited at some point in the ability to do a quality study, interact with the patient and the patient's family and provide assurance that the records are accurately kept. Just what the ceiling number should be is uncertain and is likely to be criticized by some operators. Cardiac catheterization laboratories have been spared from regulations of environmental and radiation safety. The grace period will end in the 1990s as we receive a very critical look from both government and public environmental safety groups regarding radiation hazards to operators, laboratory personnel and patients. We will also be criticized for our contribution to toxic chemicals in waste water resulting from film processing. Fortunately, the filmless laboratories will help to reduce the radiation exposure and waste water problems.

Reimbursement issues will become a major problem in the next decade. Unbundling issues have already surfaced, and more and more limitations will be placed on reimbursement for procedures that we perform. We will be very restricted in our ability to bill and collect for multiple procedures. This will be particularly true when procedures are done during the same hospitalization and certainly when they are done during the same day. In addition, I think that the Peer Review Organization will place a greater emphasis on quality indicators and that these results will have a direct relation to our ability to be reimbursed.

ETHICAL ISSUES

Perhaps the most important area in the 1990s will be ethics. There is a tremendous increase in concern among the public and government about ethical practices in general, and about ethical practices in medicine in particular.[4] Being perceived as having an ethical conflict is just as bad as being guilty of unethical practices. The public will not tolerate perceived unethical medical practices. This has tremendous ramifications in terms of the catheterization laboratory, and involves advertising in laboratories, self-referral and conspiring to corner areas of a referral market. Industry is a partner in this problem. New devices are often placed in the hands of laboratory operators who see such devices as marketing tools used to advertise their laboratories. Such practices will come under increasing scrutiny and legislation will be aimed at limiting them.

In summary, I have provided an overview of where I predict the practice of cardiac catheterization will be in the 1990s, highlighting some new areas as well as interesting old areas. Ethics is of critical concern to all of us. We will have to successfully resolve the growing regulatory and ethical problems.

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Clinical Cardiovascular Magnetic Resonance Imaging

Ronald M. Peshock, MD

Magnetic resonance imaging (MRI) is a powerful tool providing high-resolution images of the heart and great vessels without the use of ionizing radiation or contrast agents. MRI systems currently in use at many hospitals can be used effectively in the routine, clinical evaluation of many forms of cardiovascular disease, including great vessel disease, ischemic cardiac disease and congenital cardiac disease. Moreover, quantitative and cine MRI techniques are now available, which provide highly accurate measures of chamber size, wall motion and wall thickening. Recent developments in the areas of myocardial tagging, high-speed imaging and MR assessments of flow and perfusion suggest potential for an increasing role of MRI in the clinical evaluation of the cardiovascular system.

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Magnetic resonance imaging (MRI) is a powerful and flexible tool for the evaluation of the cardiovascular system. It can provide high-resolution images without the use of ionizing radiation or contrast agents and is intrinsically sensitive to flow. These features make MRI of potential use in a variety of clinical conditions, including great vessel disease, ischemic cardiac disease and congenital cardiac disease.[1] The purpose of this review is to: (1) provide a brief introduction to the basic principles of MRI; (2) describe the practical clinical applications; and (3) discuss several recent significant developments.

BASIC PRINCIPLES

The basic principles of MRI have been extensively reviewed.[2,3] Briefly, magnetic resonance has 3 requirements. First, the presence in the body of atoms whose nuclei have a magnetic moment—meaning that the nucleus of each atom will behave like a tiny bar magnet when exposed to an external magnetic field. In the case of MRI, these are nuclei of hydrogen atoms in water and fat. Second, an external magnetic field to align these nuclei is required. This is achieved by using a large magnet surrounding the patient. Third, a radio transmitter/receiver to produce a second external magnetic field that changes the orientation of the nuclear magnets and follows their return to the original orientation is necessary. This is done using a coil of wire placed close to the patient. All MRI and MR spectroscopy involves the changes in orientation of these tiny nuclear magnets by external magnetic fields.

These steps are illustrated in Figure 1. The tiny bar magnets (the nuclei of hydrogen atoms in the body in the case of MRI) are normally randomly oriented. When placed in an external magnetic field, the nuclear magnets tend to line up with the external field. If these nuclei are then exposed to a second magnetic field (provided by the radio transmitter) perpendicular to the original magnetic field, the nuclei can be tipped from their original orientation. If this second magnetic field is then turned off, the nuclei gradually return to the original orientation. As they return to the original orientation, they induce a current that can be detected. The energy released during the return of the nuclei to the original orientation is used to form the image in MRI.

By varying the timing, orientation and strength of magnetic fields to which the nuclei are exposed, it is possible to obtain a wide range of image contrasts. This is illustrated in Figure 2 for 2 techniques commonly used in clinical cardiovascular MRI: spin-echo imaging and cine MRI. Note that each of these images is obtained without the use of contrast agent. The differences in contrast between the blood and other structures is obtained by

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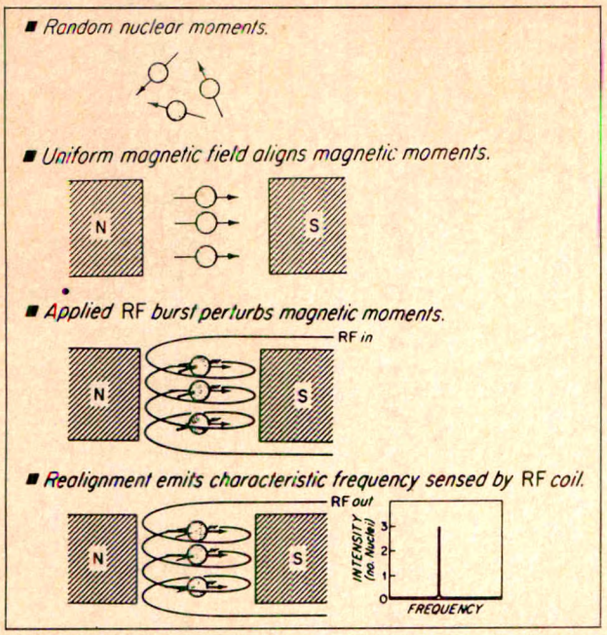


FIGURE 1. Basic principles of magnetic resonance imaging. See text. N = north; RF = radiofrequency; S = south. (Reproduced with permission from *Am J Cardiol.*[25])

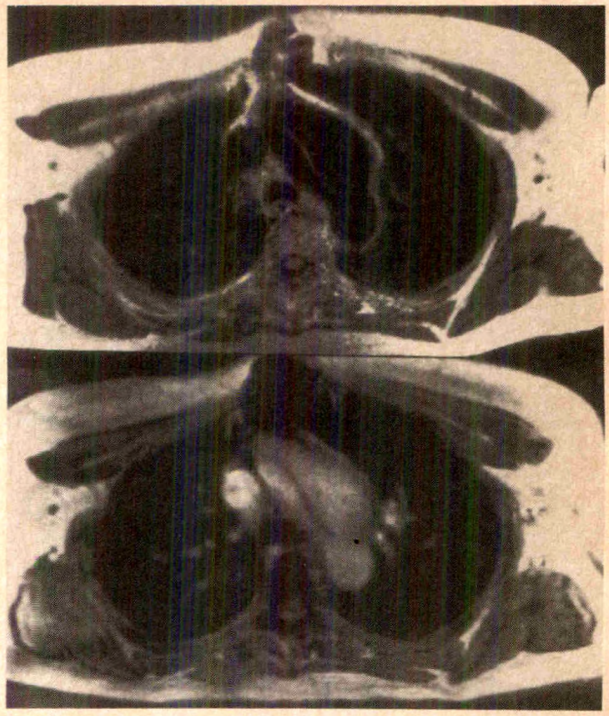


FIGURE 2. Spin-echo versus cine magnetic resonance imaging images. Transaxial images obtained through transverse portion of the aortic arch in a patient with aortic dissection using spin-echo *(top)* and cine magnetic resonance imaging *(bottom)* techniques. The intimal flap is demonstrated using both techniques.

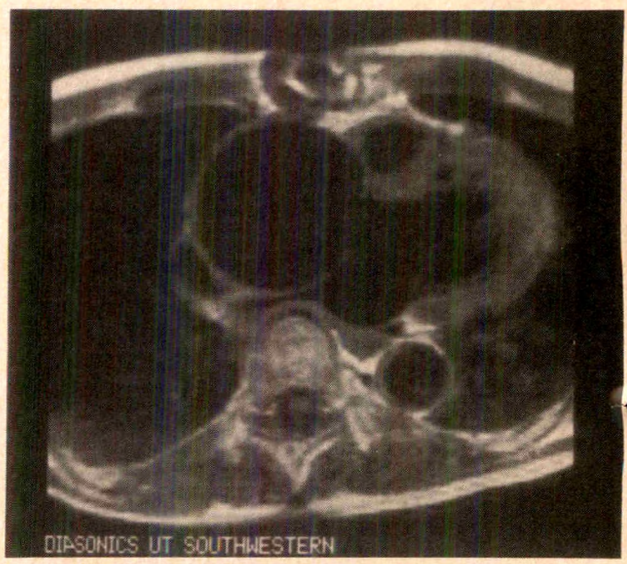


FIGURE 3. Spin-echo image in a patient with annuloaortic ectasia with a markedly dilated aortic root.

simply altering the magnetic field pulses that are applied. At present, spin-echo MRI is used primarily to obtain high-resolution structural images, whereas cine MRI is usually used to obtain functional images. In general, the spin-echo method is used to obtain multiple slices through the heart and great vessels, whereas the cine MRI method is used to obtain 1 or a few slices at multiple points in the cardiac cycle to examine aspects of motion and flow.

Currently, the presence of a cardiac pacemaker, a ferromagnetic cerebral aneurysm clip, cochlear implant, or a metal fragment in the eye are considered contraindications for MRI. Patients with sternal wires, clips used in coronary artery bypass grafting, and prosthetic cardiac valves can generally be safely imaged.[4]

CURRENT APPLICATIONS

There are 3 general areas of current clinical application for cardiovascular MRI: (1) great vessel disease; (2) particular aspects of ischemic cardiac disease; and (3) congenital cardiac disease. Again, these applications have been the subject of a number of recent, extensive reviews.[5,6] Our purpose is only to provide a brief, practical review.

The use of cardiovascular MRI is best established in the evaluation of disease involving the great vessels. In particular, aortic dissection, aortic aneurysm, congenital abnormalities of the great vessels and vena cava obstruction have been extensively studied. An example of an image obtained in a patient with aortic dissection is shown in Figure 2 using both spin-echo and cine MRI techniques. The intimal flap is evident, using both imaging techniques. Typically, standard multislice, spin-echo imaging is used to evaluate the extent of dissection with a large number of slices, while cine MRI is performed at selective levels to allow evaluation of flow in the true and false channels. In the hands of experienced users, the sensitivity of MRI in the diagnosis of dissection is comparable to that of x-ray computed tomography.[7]

MRI has also been shown to be useful in the evaluation of aortic aneurysm. Figure 3 shows a spin-echo im-

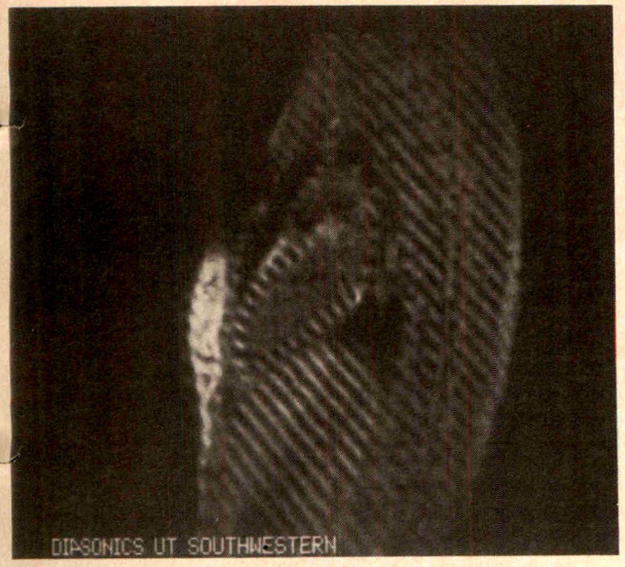


FIGURE 4. Myocardial tagging using spatial modulation of magnetization (SPAMM). The *tagging lines (dark)* were applied at end-diastole. With cardiac motion, the *tagged points* move relative to the *tagged lines* in stationary tissue allowing the determination of absolute cardiac wall motion.

age obtained in a patient with anuloaortic ectasia and clearly demonstrates the dilated ascending aorta. In Marfan's syndrome, MRI can be used to follow aortic size and to determine whether aortic dissection has occurred.[8] MRI, with its lack of ionizing radiation, may be particularly useful in the evaluation of pregnant women with Marfan's syndrome in whom dissection is a consideration. The technique typically uses gated, multislice, spin-echo imaging to cover the region of the aneurysm with cine MRI to examine aspects of flow.

Coarctation of the aorta has also been extensively studied using MRI.[9] Typically, transaxial spin-echo images are obtained to determine the minimum diameter of the aorta, with parasagittal spin-echo imaging performed along the long axis of the descending aorta to establish the extent of the narrowing. In this way, MRI can be used to establish the initial diagnosis, determine the adequacy of surgical repair and evaluate potential complications such as pseudoaneurysm.

MRI offers significant potential in the evaluation of ischemic cardiac disease.[10] MRI can obtain a complete 3-dimensional dataset without the limitations of acoustic window or need for ionizing radiation. Hence, in cases where other imaging modalities are technically limited, MRI can be used to examine the heart for regions of wall thinning and intracardiac thrombus. In addition, using multislice, multiphase and cine MRI methods, one can readily obtain assessments of chamber size, myocardial mass, wall motion and wall thickening.[11] MRI can also be used to detect regions of acute infarction, due to its inherent sensitivity to changes in tissue water content that occur in the setting of infarction.

The application of MRI in the evaluation of congenital cardiac disease has been extensive.[12] It can be particularly useful in the evaluation of malrotations of the heart and assessment after surgery. Although ultrasound is the primary modality in the evaluation of congenital cardiac disease, MRI can be a useful tool in a number of situations. These include the assessment of patients with complex congenital cardiac disease, pulmonary atresia, and palliative shunts and conduits. It is also useful in older children, adults, and patients after surgery in whom acoustic windows may be limited for ultrasound.

RECENT DEVELOPMENTS

Recently, there have been a number of developments that may lead to the increased application of MRI in clinical cardiology. The first is in the area of myocardial "tagging."[13] Standard evaluation of wall motion and wall thickening by ventriculography or echocardiography requires the identification of a given myocardial segment at multiple points in the cardiac cycle. Proving that the same segment is being evaluated at both end-systole and end-diastole requires the attachment of some physical marker to the myocardial tissue. In the case of cine angiography, this has required the attachment of beads or clips to the myocardium.[14] However, there has been no noninvasive means of applying such markers. In MRI, it is possible to apply additional pulses of energy to label or tag given portions of the myocardium. The absolute motion of these tags can then be used to measure wall motion and wall thickening unequivocally. Additional variants of this method (Fig. 4) can be used to label many points in the heart simultaneously for rapid assessment of wall motion.[15] These methods allow unambiguous evaluation of cardiac segmental function and should become the "gold standard" for assessing wall motion and wall thickening.[16]

The second major development relates to the availability of high-speed MRI. Conventional MRI of the



FIGURE 5. Echo-planar magnetic resonance imaging. Image of the heart obtained in approximately 30 ms using echo-planar magnetic resonance imaging (obtained in collaboration with Drs. Richard Rzedzian and Ian Pykett at Advanced NMR Systems, Inc.).

heart requires gating because of the time needed to collect all of the information to construct a complete image. Standard spin-echo and cine MRI sequences acquire a series of images in a period of approximately 4 to 6 minutes. Recently, a number of techniques have emerged that allow imaging of the heart using MRI in a fraction of a second. The most rapid method currently available is called echo-planar MRI and can acquire an entire image in approximately 30 ms.[17] An example of an echo-planar image is shown in Figure 5. There is some loss of resolution compared to standard images; however, the effect is small considering that the imaging time has been shortened by a factor of approximately 10,000. Unfortunately, this very-high-speed imaging requires a specialized MRI system not currently widely available.

Another form of rapid imaging is termed turbo-FLASH and acquires an image in approximately 300 ms.[18,19] This form of high-speed imaging can be implemented on many conventional MRI systems and could become more widely available in the near future.

The final area of recent development involves assessments of blood flow and perfusion. Because MRI is intrinsically sensitive to motion, it is possible to accentuate the effects of blood motion and obtain angiographic-like images. MR angiography is undergoing rapid development for the noninvasive evaluation of cerebral and peripheral vascular disease.[20] Paramagnetic contrast agents (discussed in more detail by Wolf[21] in this supplement), which distribute into tissue on the basis of blood flow, can be used to alter local tissue relaxation times and, hence, provide a means to assess regional flow. With the development of faster imaging techniques, it is possible to obtain at least qualitative estimates of tissue blood flow.[22–24]

In conclusion, numerous studies now support the use of MRI in cardiovascular imaging. In particular, MRI is an effective tool in the evaluation of patients with great vessel disease, ischemic cardiac disease and congenital cardiac disease. Importantly, MRI is now widely available, with over 1,500 units operating in the United States alone. Recent developments in the areas of myocardial tagging, high-speed imaging and assessments of perfusion suggest an increasing role for MRI in the evaluation of cardiovascular disease in the future.

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Clinical Nuclear Magnetic Resonance Spectroscopy: Insight into Metabolism

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Nuclear magnetic resonance (NMR) spectroscopy can nondestructively evaluate changes in metabolites with different disease states, as well as with therapeutic interventions. Animal studies have provided the basis for understanding changes in high-energy phosphates with myocardial ischemia. Studies of graded ischemia due to partial coronary stenosis have shown the sensitivity of the ratio of phosphocreatinine to inorganic phosphate to small reductions in myocardial blood flow and its relation to myocardial function. The application of NMR spectroscopy to humans requires precise localization techniques to avoid acquiring contaminating information from structures around the heart, such as the chest wall and diaphragm. With these localization techniques, metabolic evidence of ischemia has been demonstrated in patients with myocardial infarction and patients with known coronary disease, although the sensitivity of this technique for the diagnosis of inducible ischemia is unknown. At rest, patients with dilated and hypertrophic cardiomyopathies often have an elevated phosphodiester resonance, possibly signifying abnormal breakdown of membrane phospholipids. Increasing oxygen demand in these patients does not usually alter high-energy phosphates, suggesting that oxidative energy metabolism is preserved under these conditions. NMR spectroscopy is a powerful tool to increase understanding of metabolic changes in a variety of pathologic conditions.

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Nuclear magnetic resonance (NMR) spectroscopy is a valuable tool for the nondestructive evaluation of metabolism.[1] Using the spin properties of nuclei within a magnetic field, NMR spectroscopy can evaluate the concentrations of multiple metabolic compounds in tissues. It can thus define the changes in these compounds with different disease states, as well as with therapeutic interventions. Spectroscopy has, in the past, produced spectra representing these compounds, while NMR imaging has provided images of anatomic structures. Recent advances in NMR spectroscopy are providing images of metabolic compounds that roughly correspond to those obtained by conventional imaging.

While its usefulness as a research tool in studies of animal models of human disease is clear, the application of NMR spectroscopy to humans has been slow. This is primarily due to the difficulty of acquiring spectra from the heart and the lack of specificity of metabolic changes for different disease states. Relatively precise localization techniques must be used to avoid acquiring contaminating information from structures around the heart, such as the chest wall and diaphragm. Hence, techniques such as rotating frame, depth resolved surface coil spectroscopy (DRESS), image-selected in vivo spectroscopy (ISIS) and spectroscopic imaging (SI) have been developed to define regions of data acquisition. Interpretation of results in humans requires an understanding of the strengths and limitations of these techniques. This brief review will focus on phosphorus-31 spectroscopy and summarize the existing data and potential clinical applications of this technique for the evaluation of cardiac disease in humans.

PRINCIPLES OF NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

NMR spectroscopy examines relatively large volumes of tissue and obtains detailed information on the concentration and chemical environment of the chosen nucleus within the sample. The NMR experiment for spectroscopy is conceptually much simpler than the imaging experiment familiar to most readers. Within a uniform applied magnetic field, the tissue is excited by a radio frequency pulse near the resonant frequency of the nuclei of interest. After this excitation, the nuclei reorient themselves back into the axis of the magnetic field, giving off energy and hence emitting a signal that decreases exponentially with time, called a free induction decay (FID). After detection of this signal, a mathematical operation called a Fourier transformation is performed to define the intensity of different frequency components of the FID. If all the nuclei of interest are chemically identical, the FID will have only 1 frequency and the resulting Fourier transfor-

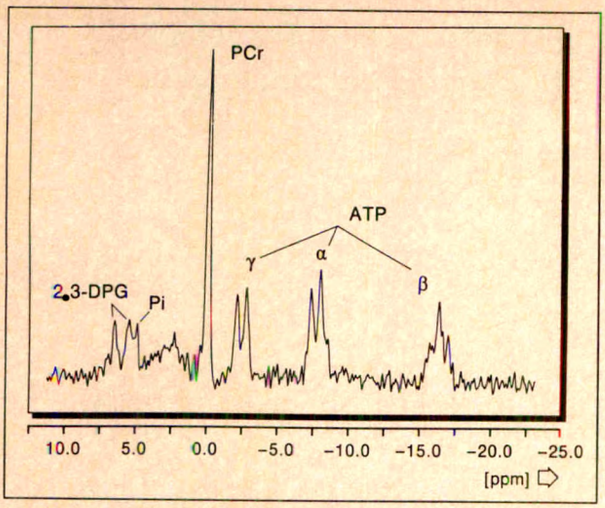


FIGURE 1. A spectrum from a human heart acquired at 1.5 Tesla with image-selected in vivo spectroscopy (ISIS) for localization and proton decoupling to enhance resolution. This spectrum demonstrates the resonance from blood 2,3-diphosphoglycerate (2,3-DPG), inorganic phosphate (Pi), phosphocreatine (PCr) and adenosine triphosphate (ATP). PPM = parts/million. (Reproduced with permission from *NMR in Biomed.*[11])

mation will have only 1 peak whose intensity is proportional to the strength of the signal. If, however, the nuclei are in several different chemical environments, the FID will have a number of frequency components and its Fourier transformation will have several peaks, each proportional to the strength of the signal at that resonant frequency. This representation of intensity (on the y-axis) versus frequency (on the x-axis) is termed the spectrum (Fig. 1).

The presence of species with different resonant frequencies in the spectrum is due to a phenomenon termed "chemical shift." As previously noted, the resonant frequency of a nucleus is proportional to the magnetic field applied to it. In addition to the main magnetic field, each nucleus is subject to a small magnetic field produced by the electrons surrounding it. This local electron-induced field changes the resonant frequency of that nucleus slightly, a change termed chemical shift since the electron distribution is altered by the chemical status of the nucleus. The chemical shift difference between one resonance and another is defined in Hz (frequency), and increases with increasing field strength. For uniformity, chemical shift is often expressd in parts per million (PPM), a number that is independent of the applied field strength. Chemical shift allows the identification of different peaks in a spectrum, since each peak is formed by the nucleus of interest in a slightly different chemical environment. For example, in the normal cardiac spectrum in Figure 1, the β phosphate of adenosine triphosphate has a resonant frequency that differs from the phosphate in phosphocreatine by approximately 16 PPM, thus allowing its identification.

The spectrum also provides information about concentrations of the various species, since the intensity of each of the defined peaks is proportional to the number of nuclei in that chemical environment. Although conceptually simple, this analysis may be complicated by the fact that different molecules may have exactly the same resonant frequency, as in the overlap of the resonances of adenosine diphosphate with the α and γ resonances of adenosine triphosphate. If a standard is available, absolute concentrations of each molecule can be calculated. However, in in vivo spectroscopy, relative concentrations are often used due to the technical difficulties in obtaining accurate standardization.

Principles of chemical shift can also be used for noninvasive measurement of intracellular pH. In some molecules, the electron distribution, and therefore resonant frequency, is sensitive to, and changes with, pH. Notably, the state of orthophosphate (HPO_4^- or H_2PO_4) is pH-dependent and its chemical shift with respect to phosphocreatine (which is not pH-dependent) is a function of intracellular pH. Thus, the change in pH of a tissue can be serially examined after interventions or during disease states.

METABOLIC PATHWAYS STUDIED BY NUCLEAR MAGNETIC RESONANCE

The myocyte, with abundant mitochondria, is well adapted for the metabolic demands of repeated muscle contraction. Since the heart is an extremely oxidative tissue and normally generates only a small fraction of its energy from glycolysis, most of the adenosine triphosphate is produced in the mitochondria by oxidative phosphorylation (Fig. 2). Hydrolysis of adenosine triphosphate by actomyosin adenosine triphosphatase provides the energy for muscle contraction, while some adenosine triphosphate is used to drive adenosine triphosphate-dependent pumps (such as sodium-potassium exchange and

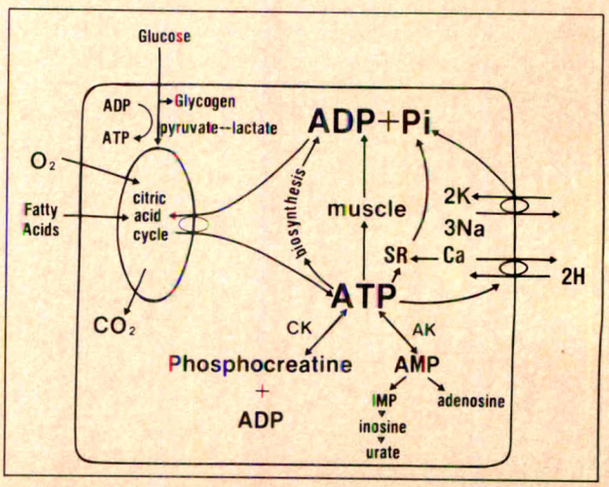


FIGURE 2. The metabolic pathways in the myocyte supplying ATP. Phosphorus-31 NMR spectroscopy can measure relative concentrations of Pi, PCr and ATP, allowing calculation of intracellular pH (from the chemical shift of Pi) and the concentration of adenosine diphosphate (ADP), as well as reaction rates such as creatine kinase (CK) flux AMP = adenosine monophosphate; AK = adenosine kinase; H = hydrogen; K = potassium; NA = sodium; SR = sarcplasmic reticulum; other abbreviations as in Figure 1.

calcium uptake into the sarcoplasmic reticulum). The rate of adenosine triphosphate synthesis is thought to be regulated by: (1) the availability of oxygen; (2) the availability of substrates to the citric acid cycle so that nicotinamide-adenine dinucleotide is generated by various dehydrogenases; and (3) the availability of adenosine diphosphate as a substrate to synthesize adenosine triphosphate.

The ability of NMR to examine these various metabolic pathways stems from the number of different nuclei available for study. The most commonly used nucleus, phosphorus-31, allows measurement of the concentrations of adenosine triphosphate, phosphocreatine and inorganic phosphate, as well as calculation of intracellular pH and adenosine diphosphate concentration. Using specialized techniques such as magnetization transfer, fluxes in 1 or more reactions, such as the creatine kinase reaction, can also be measured. The involvement of the phosphorus nucleus in such important biologic processes, as well as its relative ease of measurement, has made it the most commonly studied nucleus by NMR. Hence, much of the work cited in this review will focus on studies using phosphorus-31.

The hydrogen nucleus, or proton, is much more abundant and easily studied than phosphorus, leading to its use in conventional NMR imaging. However, proton NMR can also be used to acquire spectra[2] that can be used to quantitate such metabolites as lactate, creatine, choline and N-acetyl aspartate. Difficulties with proton NMR include: (1) the requirement to suppress a large water signal and, in some tissues, a large lipid signal to visualize the metabolite resonances; and (2) the relatively small differences in chemical shift between metabolite resonances, making isolation and identification of these resonances more difficult. Despite these difficulties, studies of human brain and heart are now being performed with some success.

Carbon-12 is abundant in the human body but is, unfortunately, not amenable to observation by NMR. Carbon-13 is NMR-sensitive and can be exogenously administered. Cardiac studies using carbon-13 NMR in perfused hearts have examined metabolic pathways in the citric acid cycle,[3] but the relative insensitivity of the experiment, as well as the cost of carbon-13, have precluded human cardiac studies. However, this agent has been used to measure glucose utilization elegantly in normal and diabetic humans.[4]

NUCLEAR MAGNETIC RESONANCE STUDIES IN ANIMALS AND HUMANS

Animal studies (ischemia and infarction): The metabolic response of the myocardium to ischemia and infarction has been characterized using both biochemical and NMR techniques. With reduction of blood flow, phosphocreatine decreases, inorganic phosphate increases and intracellular acidosis ensues. Adenosine triphosphate also decreases, but at a slower rate and degree, depending on the availability of phosphocreatine to provide adenosine triphosphate through the creatine kinase reaction.

The characteristics of these metabolic changes, and their relation to contractile function, have most recently been studied in our laboratory.[5] Using an in situ open-chest pig preparation, the metabolic changes during and after complete, but brief, coronary artery occlusion were measured. Signal averaging over multiple interventions allowed reconstruction of spectral data with 5-second time resolution. As seen in Figure 3, the expected changes in phosphocreatine, inorganic phosphate and adenosine triphosphate occurred during this 24-second period, along with a rapid decline in function (defined by segment shortening). These abnormalities resolved after release of the occlusion with a time course different from that of reactive hyperemia, suggesting dissociation of coronary flow from metabolism in this period. Also, metabolism remained unchanged for 5 seconds after occlusion, possibly due to the oxygen available in myocardial myoglobin. These data, in addition to lending insight into basic biologic processes, may also provide the basis for therapeutic intervention studies.

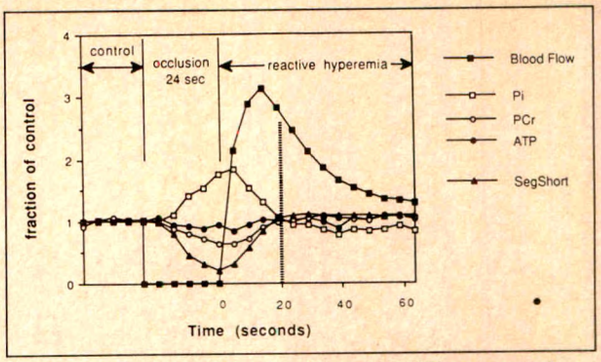


FIGURE 3. The response of coronary blood flow, segment shortening (Seg Short) and phosphorus metabolites (PCr, Pi and ATP) to a 24-second coronary artery occlusion followed by release. During the ischemic period, there was a rapid change in metabolites that paralleled the change in segment shortening. On reperfusion, both metabolism and function returned to control values well before coronary flow. Abbreviations as in Figure 1. (Reproduced with permission from the American Heart Association.[5])

Since many patients have established coronary stenoses with reduced, but not absent, flow, the metabolic and functional responses to steady-state reductions in coronary flow were examined.[6,7] Again using an open-chest porcine model and surface coil NMR, coronary blood flow, and hence regional myocardial blood flow, was incrementally reduced by constriction of the left anterior descending coronary artery. As with total coronary artery occlusion, reduction of blood flow caused reduction of phosphocreatine and pH, with a concomitant increase of inorganic phosphate. There was a close relation between phosphocreatine/inorganic phosphate (a measure of the energy reserve of the heart) and blood flow and segment shortening over the range of ischemic conditions (Fig. 4), suggesting a relation between metabolism and function under these conditions. Also, phosphocreatine/inorganic phosphate was a sensitive indicator of regional ischemia and thus may be useful as a parameter to follow in human studies.

Phosphorus-31 NMR may also have application in

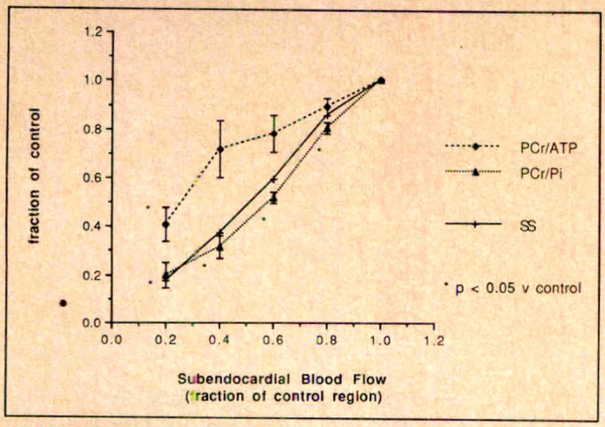


FIGURE 4. The relation of the metabolic and functional response to graded steady-state regional ischemia in the pig. As myocardial blood flow was reduced from control levels, both phosphate metabolism, as measured by the ratio of PCr/Pi, and function, as measured by segment shortening (SS), were reduced in concert. PCr/Pi was significantly correlated to subendocardial blood flow (r = 0.94) and SS (r = 0.94). Abbreviations as in Figure 1. (Reproduced with permission from *J Clin Invest.*[7])

the clinical differentiation of infarcted from viable myocardium. Rehr et al,[8] in a dog model of coronary occlusion, measured high-energy phosphates in normal, ischemic and reperfused tissue. They found that effective separation of these 3 conditions could be achieved with an accuracy of 89% using pH and the ratios of phosphocreatine/adenosine triphosphate, inorganic phosphate/adenosine triphosphate and inorganic phosphate/phosphocreatine. Wolfe et al[9] were also able to differentiate infarcted from reperfused myocardium in the rat and, furthermore, were able to correlate these findings with abnormalities on proton images after contrast agent administration. Hence, measurement of high-energy phosphates in humans may give insight into the metabolic status of the heart.

Human studies (normal): The aformentioned studies have all used a surface coil directly on the heart, a technique not well suited for human studies. Therefore, a great deal of effort has been directed toward acquiring spectra from the heart using a coil on the body. These efforts have primarily focused on surface coil localization techniques, such as DRESS,[10] ISIS,[11,12] rotating frame[13] and SI,[14] and each of these techniques has been used to acquire spectra from humans.

The first human spectrum was acquired from an 8-month-old child with a congenital cardiomyopathy and showed metabolic abnormalities that corrected with therapy.[15] Bottomley[16] then used the DRESS localization technique to acquire cardiac spectra from normal humans, followed by Blackledge et al[13] and Schaefer et al,[17] in studies that established the feasibility of acquiring localized spectra from the human heart. These studies were important in defining the normal values of high-energy phosphates in the human heart and in demonstrating the various advantages and disadvantages of different techniques in acquiring spectra. Recently, 3-dimensional SI has emerged as a localization technique that allows the generation of metabolic maps of organs, similar to the proton maps we read as images in NMR imaging. In this technique, magnetic field gradients are used to encode spatially the spectral information in 3 dimensions. Usually, 2-dimensional images of the distribution of phosphocreatine or adenosine triphosphate, for example, are reconstructed from a number of slices through an organ, although the 3-dimensional data set can theoretically be displayed in its entirety. While not achieving the resolution of conventional proton imaging (the average voxel is 2 × 2 × 2 cm), these images readily demonstrate metabolic inhomogeneities. The absence of significant motion has directed most of the 3-dimensional SI to head examinations (using either phosphorus or proton NMR spectroscopy), although surface coil 3-dimensional SI has recently been used in phosphorus cardiac studies with success.[18]

One of the important questions addressed by NMR spectroscopy centers around the regulation of myocardial metabolism when oxygen consumption is increased. Some investigators have theorized that oxidative phosphorylation in human myocardium may be regulated by the concentrations of high-energy phosphates, namely adenosine diphosphate, adenosine triphosphate/adenosine diphosphate or adenosine triphosphate/adenosine diphosphate/inorganic phosphate. Others have postulated that substrate composition (fatty acids versus glucose), calcium kinetics or hydrogenase enzyme activity regulates oxidative phosphorylation. In vivo animal studies using pacing or inotropic stimulation have demonstrated different responses in different species. For example, in one study,[19] the metabolic response of cats to increased oxygen consumption was different than that of dogs. This interspecies difference was postulated to stem from the different lifestyles of these 2 animals, with cats primarily involved in sprinting and dogs primarily involved in endurance activities. The place of humans in this schema is unknown. To address this question, we studied 7 normal subjects in our laboratory using image-localized 1-dimensional spectroscopic imaging. Baseline studies were performed over the left ventricle, followed by infusion of dobutamine to increase the rate-pressure product by 200%. Repeat spectroscopy was performed and the spectra were analyzed for changes in the ratio of phosphocreatine/adenosine triphosphate and inorganic phosphate/phosphocreatine. No significant changes in either ratio were found, thus ruling out significant changes in adenosine diphosphate. Therefore, in the normal human heart, increases in oxidative phosphorylation caused by inotropic stimulation are not mediated by changes in high-energy phosphates.

Human studies (ischemia and infarction): The investigation of cardiac disease in humans has been limited to a few preliminary studies. As noted earlier, myocardial infarction produces profound changes in high-energy phosphates. Studies of patients after myocardial infarction using DRESS have demonstrated elevations of inorganic phosphate and reductions of phosphocreatine,[20] with some suggestion that subendocardial, versus transmural,

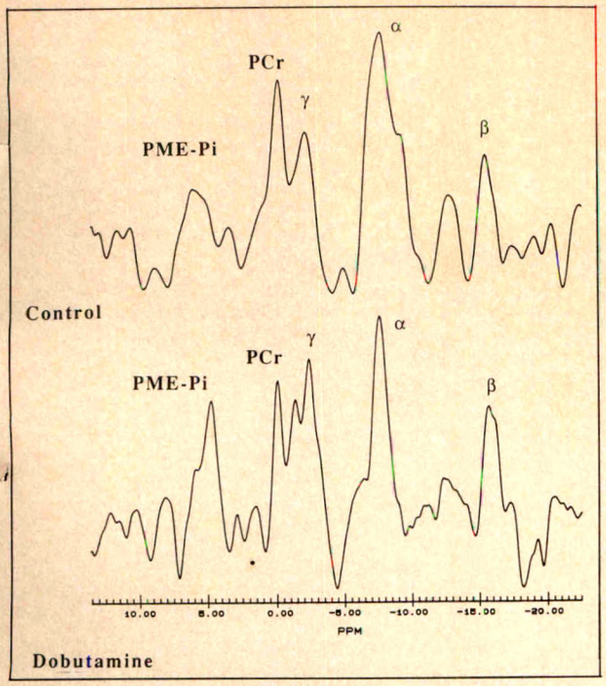


FIGURE 5. Phosphorus-31 spectra from a patient with coronary artery disease stressed using a dobutamine infusion. Under control conditions *(top)*, there is a normal relationship between phosphorcreatine (PCr), adenosine triphosphate (ATP) and inorganic phosphate (Pi). With stress *(bottom)*, there is metabolic evidence of ischemia, with a reduction in PCr and an increase in Pi similar to that seen in animal models of reduced coronary blood flow.

abnormalities could be detected. The inexact localizing ability and poor spatial resolution of spectroscopy limits its usefulness for the quantitation of infarct size, although its ability to separate infarcted from ischemic myocardium may lead to its clinical use in this arena.

The diagnosis of myocardial ischemia with phosphorus-31 NMR in man has been limited by the inability to measure accurately myocardial inorganic phosphate due to the overlapping signal from the 2,3-diphosphoglycerate of chamber blood. Thus, calculation of the ratio of phosphocreatine/inorganic phosphate, shown previously to be a sensitive marker of ischemia, is difficult in humans. Nevertheless, NMR spectroscopy is being evaluated for the detection of ischemia in humans. In patients with severe proximal coronary artery disease, Bottomley et al[21] have demonstrated alterations in high-energy phosphates with handgrip exercise that increased rate-pressure product approximately 15 to 20%. Using dobutamine to elicit myocardial ischemia, similar abnormalities in high-energy phosphates were noted in a patient studied in our laboratory with 1-dimensional spectroscopic imaging (Fig. 5). The feasibility of performing aerobic leg exercise in a magnet has previously been demonstrated,[22] along with recent acquisition of spectra during exercise in our laboratory. Although preliminary, these data suggest a role for NMR spectroscopy in the detection of myocardial ischemia. Further evolution of NMR localization techniques and stress methodologies will improve the efficacy of NMR in this setting.

Human studies (global myocardial disease): Localization requirements for the NMR examination of global myocardial disease are less stringent than in ischemic cardiac disease. Since these processes are, in general, homogenous, examination of large volumes of the heart are possible. Also, unlike ischemic cardiac disease, animal models for cardiomyopathy are inadequate. Human studies of cardiomyopathy have addressed the questions of resting abnormalities in high-energy phosphates, abnormalities elicited by stress and response after transplantation.

Two separate studies of patients with dilated cardiomyopathy[23,24] or left ventricular hypertrophy, or both, have shown that relative concentrations of phosphocreatine and adenosine triphosphate are normal under resting conditions. These studies, however, showed abnormally elevated concentrations of phosphodiesters (Fig. 6), presumably from breakdown of membrane components in patients with myocyte loss. Under stress (e.g., dobutamine infusion), patients with dilated cardiomyopathy do not show any significant change in relative high-energy phosphate concentrations,[25] suggesting that the energy reserve in these patients is maintained with increased oxygen demand.

Animal models of cardiac transplantation have also demonstrated abnormalities of high-energy phosphates that paralleled the course of rejection.[26] An important question is whether, in humans, these changes could be detected and possibly provide earlier, or at least equivalent, information to endomyocardial biopsy. Although not supported by more recent work, Herfkens et al[27] showed that changes in high-energy phosphates paralleled, and in 1 instance, preceded, histologic changes on

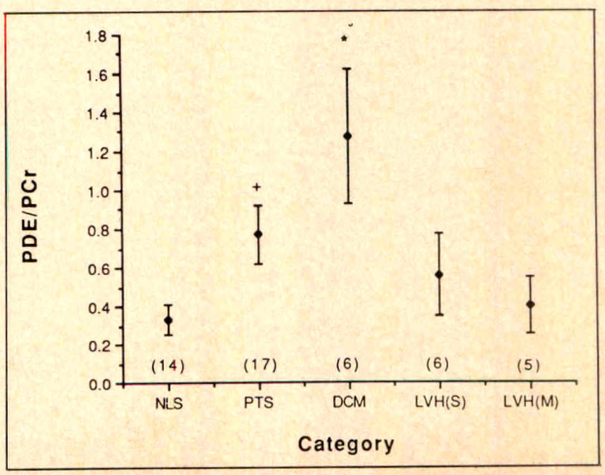


FIGURE 6. Results of phosphorus-31 spectroscopy in patients with dilated cardiomyopathy (DCM) and left ventricular hypertrophy (LVH), either mild (M) or severe (S). The ratio of phosphodiesters to phosphocreatine (PDE/PCr) was elevated in the patients (PTS) with dilated cardiomyopathy, possibly signifying myocardial cell membrane damage. *p <0.05 compared to other groups. †p <0.05 compared to normal subjects (NLS). (Reproduced with permission from *Am J Cardiol.*[23])

biopsy. Whether noninvasive NMR spectroscopy may supplant endomyocardial biopsy is unknown: however, further research into this important area is promising.

In conclusion, NMR spectroscopy, although in its early stages of application to the study of human cardiac disease, remains a promising technique. Its ability to provide insight into myocardial metabolism without exogenous tracers gives it a unique role for the investigation of pathologic as well as normal processes. NMR spectroscopy has demonstrated its ability to detect, in humans, metabolic abnormalities due to myocardial ischemia and infarction, cardiomyopathy and transplantation. Further investigation into its sensitivity and specificity for disease processes, coupled with development of localization techniques and deployment of high-field NMR systems, will demonstrate the true role of NMR spectroscopy in the future of cardiac diagnosis.

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Positron Emission Tomography and Interventional Cardiology

K. Lance Gould, MD

Current noninvasive diagnostic techniques have limited accuracy for detection of coronary artery disease (CAD) in symptomatic and (particularly) asymptomatic patients with silent disease. Furthermore, no standard noninvasive method provides reliable diagnostic information on the location of the coronary arteries involved, the severity of stenosis, the presence of collaterals and myocardial viability. Based on >1,000 cardiac studies at the University of Texas, cardiac positron emission tomography (PET) with either generator-produced rubidium-82, cyclotron-produced N-13 ammonia, or F-18 deoxyglucose is suitable for 4 routine diagnostic purposes: (1) noninvasive diagnosis of CAD in either symptomatic or asymptomatic subjects with a sensitivity of 95 to 98% and specificity of 95 to 100%. This accuracy is now sufficient to schedule diagnostic catheterization and multivessel angioplasty with surgical backup on the basis of the PET scan. At the University of Texas we carry out PET in asymptomatic and symptomatic patients to direct those with mild disease to cholesterol-lowering reversal therapy and those with severe disease to percutaneous transluminal coronary angioplasty (PTCA); (2) assessment of physiologic severity of coronary artery stenosis as compared to automated quantitative coronary arteriographic analysis. Changes in stenosis severity are followed before and after interventions including PTCA, bypass surgery, vasodilator drugs and cholesterol control regimens for reversal of coronary atherosclerosis; (3) imaging myocardial infarction, ischemia, viability, zone at risk and sizing of these pathophysiologic processes. Major therapeutic decisions such as cardiac catheterization, bypass surgery and PTCA are made on the basis of the PET scan alone when clinical and catheter information are not definitive; and (4) identification and assessment of significant collateral function in humans by imaging myocardial steal after intravenous dipyridamole.

Positron imaging provides the diagnostic basis of invasive or noninvasive medical therapy for symptoms or for preventing sequelae of CAD in specific symptomatic or asymptomatic individuals, thereby justifying the routine, clinical, economical use of PET in cardiology.

(Am J Cardiol 1990;66:51F–58F)

Coronary artery disease (CAD) causes 1.5 million myocardial infarctions and 520,000 deaths/year, or 33 to 50% of deaths in patients between the ages of 35 and 64 years in the United States.[1,2] Up to 13% of middle-aged men in the general population have coronary atherosclerosis, most of it clinically silent.[3,4] Silent ischemia is increasingly recognized in symptomatic and asymptomatic patients.[5–14] It has an unfavorable prognosis when occurring during exercise testing,[7] in patients with recent unstable angina[8] or in asymptomatic patients with perfusion defects after dipyridamole scanning.[11–14] Up to 48% of asymptomatic subjects with silent ischemia have a cardiac event (angina pectoris, myocardial infarction or sudden death) within 4 to 6 years.[7,9] Forty to 60% of patients with sudden death or myocardial infarction present without previous symptoms.[15–18] Therefore, silent coronary atherosclerosis remains a particular problem in cardiovascular medicine because there are no warning symptoms until a major cardiac event occurs.

Associated with this high prevalence of CAD, Figure 1 shows the time trends of cardiac catheterization, percutaneous transluminal coronary angioplasty (PTCA) and bypass surgery in the U.S.[2,19] The increases are exponential with a doubling time of 5 years (Fig. 2).[19] The percent of patients having diagnostic cardiac catheterization and subsequently going to mechanical intervention (PTCA or bypass surgery) has increased from 30 to 60%, shown in Figure 3.[19] These increasing numbers, despite the declining incidence of CAD[20,21] suggest that criteria for mechanical intervention have changed in recent years. The changed criteria for mechanical intervention are not related solely to growth of PTCA, because bypass surgery has also recently increased at nearly the same rate.

Traditionally, mechanical intervention has been reserved for patients with angina pectoris, or its equivalent, refractory to medical therapy. With our current pharmacopeia of calcium antagonists and β blockers, patients are uncommonly refractory to medical therapy, even those with unstable angina. Those who are unstable usually go to emergent mechanical intervention. Thrombolysis is frequently used in early myocardial infarction, followed by mechanical intervention. The trend of more effective

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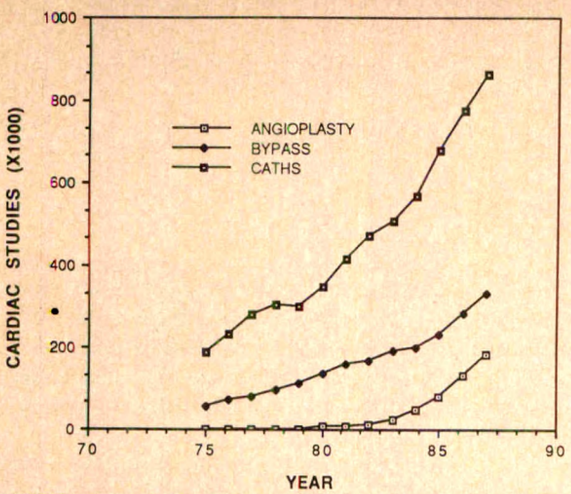


FIGURE 1. Trends in cardiac catheterization, percutaneous transluminal coronary angioplasty and coronary artery bypass surgery. (Reproduced with permission from *Coronary Artery Stenosis.*[19])

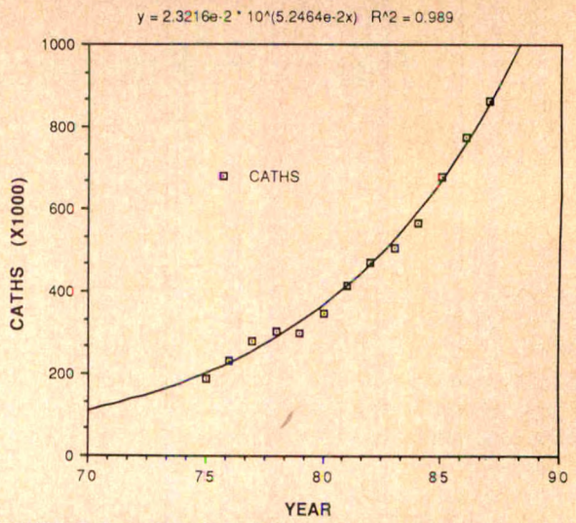


FIGURE 2. Log plot of trends in cardiac catheterization (CATHS), paralleled by percutaneous transluminal coronary angioplasty and bypass surgery with a recent doubling time of approximately 5 years. (Reproduced with permission from *Coronary Artery Stenosis.*[19])

medical therapy but increasing mechanical interventions suggests that therapeutic goals have appropriately extended to encompass more than relief of cardiac symptoms. Goals of cardiovascular therapy now include prevention of ischemia and myocardial infarction by earlier pharmacologic or mechanical reperfusion, salvage of myocardium during acute infarction, definitive restoration of coronary artery lumen, and prolonging life.

Although the goals of mechanical intervention are appropriately expanding, the clinical criteria for more frequent elective mechanical interventions in specific patients is frequently unclear. Quantitative coronary arteriography is not widely used despite the recognized limitations of percent diameter stenosis by either caliper or visual estimates. Noninvasive thallium exercise stress testing has significant limitations for diagnosing or assessing the severity of CAD or myocardial viability, as discussed subsequently.

Thus, major questions for cardiovascular medicine are how to identify silent CAD in specific patients, how to define its severity in either the symptomatic or asymptomatic patient, how to decide objectively among dietary, medical and mechanical interventions, and how to assess the results, invasively and noninvasively. At the other end of the clinical spectrum in patients with myocardial infarction, the decision to implement definitive mechanical intervention associated with significant risks (i.e., myocardial salvage by thrombolysis, PTCA or bypass surgery), requires reliable measures of myocardial viability and involvement of other coronary arteries.

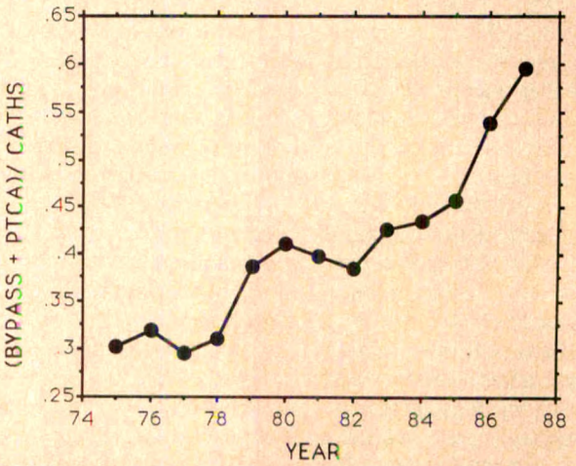


FIGURE 3. Proportion of patients undergoing cardiac catheterizations (CATHS) that subsequently go to percutaneous transluminal coronary angioplasty (PTCA) or bypass surgery. (Reproduced with permission from *Coronary Artery Stenosis.*[19])

RISK FACTORS

Risk factors do not accurately identify patients with symptomatic or asymptomatic CAD. For example, of 40- to 55-year-old men with high cholesterol and blood pressure, 67% remain well during the subsequent 25 years[22] while 33% develop CAD. In asymptomatic men of this age group with risk factors, coronary arteriography shows disease in 15 to 25%[1,3,4,23,24] that is anatomically severe in 7 to 35%.[1,24] Of middle-aged men without symptoms with a positive electrocardiographic exercise test, only 30 to 43% have significant CAD by arteriography[1] and 5 to 46% (mean 25%) develop clinical disease over the next 13 to 25 years.[1,22] Therefore, approximately 67% of men are resistant to clinical CAD despite having risk factors, while 33% develop it, often with only modestly elevated or normal cholesterol levels.

POSITRON EMISSION TOMOGRAPHY

Cardiac positron emission tomography (PET) accurately identifies and assesses severity of coronary artery stenosis and myocardial viability as a basis for choosing and following effects of interventions, including risk factor management, pharmacologic agents, PTCA, thrombolysis and bypass surgery. Accurate quantitation is particularly important in silent CAD as the only criterion for intervention to prevent sudden death or acute myocardial infarction.

Therefore, cardiac PET is not only a reliable guide to managing CAD in traditional cardiology practice based on symptoms, but also provides the basis for vigorous medical or mechanical management of asymptomatic coronary atherosclerosis. Such accurate noninvasive evaluation by PET is intended to identify patients who really need cardiac catheterization and to avoid unnecessary procedures in patients with either mild or no CAD. Cardiac PET interfaces positively with invasive cardiology by making its applications more efficient and selective.

The physiologic basis, the technology and the major clinical applications of PET have been reviewed in detail recently[19] (in a textbook on cardiac PET). Clinical and experimental studies currently support the subsquently outlined clinical applications for cardiac PET.

Noninvasive diagnosis of coronary artery disease in either symptomatic or asymptomatic patients: The sensitivity and specificity of diagnosing CAD by PET compared to automated quantitative coronary arteriography are both 95 to 98% in symptomatic or asymptomatic patients, including those with balanced 3-vessel disease. False-negative studies are usually associated with distal coronary artery stenoses or disease of the smaller arteries; false-positive studies are usually associated with nonatheromatous coronary artery abnormalities such as spasm or thrombi.[19]

Assessment of the physiologic severity of coronary artery stenosis or changes in stenosis severity: As previously reviewed,[19] percent diameter narrowing is not an adequate standard for quantifying severity of coronary artery narrowing. It does not account for the effects of diffuse disease, eccentricity, stenosis length, absolute cross-sectional area, entrance and exit shape, and absolute dimensions on flow or flow capacity. It is also limited by substantial inter- and intraobserver variability. Alternative invasive measurements of graded stenosis severity use quantitative arteriographic methods to calculate stenosis resistance, pressure-flow curves or coronary flow reserve.[19]

The quantitative severity of PET perfusion defects after dipyridamole parallel the anatomic severity of the coronary artery stenosis as determined by automated, quantitative coronary arteriography, taking into account length, absolute dimensions, shape and percent narrowing of the stenosis. Therefore, noninvasive PET provides assessment of the physiologic severity of coronary stenoses as well as changes in severity after an intervention such as thrombolysis, bypass surgery, PTCA or cholesterol lowering.

With accurate quantitation of stenosis severity, binary analysis based on sensitivity and specificity becomes inadequate or even misleading for validating or describing diagnostic value. Consequently, this capacity of PET for quantifying functional stenoses severity is one of its unique strengths, demonstrable by comparison to an appropriate arteriographic "gold standard" that takes into account all stenosis dimensions. Comparison of two noninvasive methods, e.g., PET versus single photon emission computed tomography (SPECT), using arteriographic percent diameter stenosis as the standard may be misleading or may inappropriately favor one or the other noninvasive method, since percent stenosis has little relation to coronary flow reserve except for very severe narrowing.

Imaging myocardial ischemia, infarction and viability: The location and extent of myocardial infarction and myocardial ischemia or viability may be imaged by PET with or without reperfusion using generator-produced rubidium-82 or cyclotron-produced N-13 ammonia and F-18-fluorodeoxyglucose to determine whether bypass surgery or PTCA is indicated.[19]

Identification and assessment of significant collateral function in humans by imaging coronary steal during dipyridamole-handgrip: Coronary steal occurs under conditions of near maximum coronary vasodilation of collaterals providing a significant proportion of resting myocardial perfusion. A decrease in absolute myocardial uptake of activity after injection of a perfusion tracer during dipyridamole vasodilation as compared to rest indicates coronary steal and the presence of significant collateral vessels. Since significant collaterals develop only with nearly occluded or completely occluded coronary arteries, identification of steal by PET also implies severe stenoses or occlusion.[19]

EXAMPLE OF PHYSIOLOGIC INFORMATION IN A CLINICAL POSITRON EMISSION TOMOGRAPHY SCAN

Three-dimensional topographic maps of myocardial perfusion are shown in Figure 4.[19] The patient was a 53-year-old asymptomatic man with a normal thallium scan and electrocardiographic treadmill test 10 days and 1 year before the PET scan. The rest PET study is shown in the upper row (S1) and the dipyridamole study is shown in the lower row (S2). Each panel of the topographic map views the left ventricle as if looking at the septum (first panel), at the anterior wall (second panel), at the left lateral wall (third panel) or the inferior wall (fourth panel). The dashed white line marks the upper limit of automated quantitative data, since the membranous septum often causes a normal defect at the atrioventricular ring. The black dashed lines delineate septal, anterior, lateral and inferior quadrants, with the lower dashed line delineating the apex. The colored scaling and automated quantitation, such as minimum activity values, mean activity in each quadrant, and percent of myocardium beyond 1.5, 2.0 and 2.5 standard deviations, are all the same as previously described for polar maps.[19]

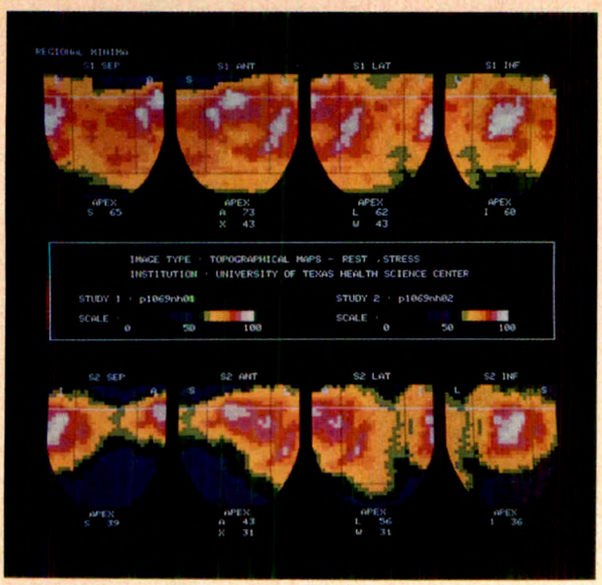


FIGURE 4. Three-dimensional topographic display of a positron emission tomography image of left ventricular perfusion using generator-produced rubidium-82. See text for details. (Reproduced with permission from *Coronary Artery Stenosis.*[19])

In Figure 1, the rest image (top row) showed a mild small apical defect, suggesting a small, old, apical myocardial infarction despite absence of a clinical event. The dipyridamole image (bottom row) showed a large severe anterior and apical defect involving 29% of myocardium outside 2.5 standard deviation from normal. There were definite but less severe defects of the anterior septum and lateral wall. These results were interpreted as showing a severe mid-left anterior descending (LAD) stenosis, another less severe LAD stenosis proximal to the first septal perforator, and a moderate stenosis of an artery to the lateral myocardial wall, probably a left circumflex stenosis. Left ventricular function was normal.

Accordingly, the patient was scheduled for diagnostic catheterization and PTCA of 3 stenoses with surgical backup. Quantitative coronary arteriography confirmed a severe stenosis of the mid-LAD artery, a moderately severe narrowing of the proximal LAD artery, and a moderately severe stenosis of the mid-left circumflex artery. PTCA was carried out on these 3 lesions due to severity of the disease over a large extent of myocardium.

REVERSAL OF CORONARY ATHEROSCLEROSIS

The question often arises whether accurate detection of coronary atherosclerosis is clinically useful, particularly in asymptomatic subjects. Although overwhelming epidemiologic evidence links CAD to smoking, serum cholesterol, hypertension and family history, large trials of modest risk factor modification with mortality end points have been somewhat disappointing without the expected definitive benefit on mortality, as recently reviewed.[19] In contrast with these previous large clinical trials, our randomized arteriographic trial,[19,25,26] the Cholesterol Lowering Atherosclerosis Study (CLAS) study by Blankenhorn et al,[27] and the Familial Atherosclerosis Treatment Study (FATS) trial by Brown et al[28] demonstrate that partial reversal of coronary artery stenosis is feasible in humans.

Our study was a randomized, controlled, blinded, arteriographic trial to determine the effects of strict risk factor modification on the geometric dimensions, shape and fluid dynamic characteristics of arteriographic coronary artery stenoses in humans.[19,25,26] Using percent diameter stenosis as the end point is the most widely recognized measure of stenosis severity. We demonstrated cessation of progression or regression in approximately 80 to 85% of treated patients compared to approximately 80 to 85% progression in the control group. However, complex changes of different stenosis dimensions in opposite directions or to different degrees may cause stenosis shape change with profound effects on fluid dynamic severity, not accounted for by simple percent narrowing. Accordingly, we analyzed all stenosis dimensions on coronary arteriograms (including absolute proximal, minimal, distal diameter [area], percent stenoses, integrated length and exit effects) to determine stenosis shape and a single integrated measure of functional severity, stenosis flow reserve, incorporating the fluid dynamic effects of all these dimensions. In the control group, complex shape change and stenosis molding characteristic of statistically significant progressing severity occurred with worsening of stenosis flow reserve. In the treated group, complex shape change and stenosis molding characteristic of significant regressing severity was observed with improved stenosis flow reserve.[19] These results document for the first time the multidimensional characteristics of regressing coronary artery stenoses associated with risk factor modification in humans.

However, marked lifestyle change[25,26] or lowering of serum cholesterol with multiple drugs[27,28] is necessary to prevent progression or reverse severity of coronary artery stenoses with reasonable certainty in individual patients. Such vigorous lifestyle changes or drug interventions may not be appropriate for these patients with risk factors who do not have coronary artery stenosis. Those patients who have CAD or a genetic predisposition to CAD may need more aggressive risk factor interventions than indicated or possible for the general population or for patients with modestly elevated cholesterol without coronary artery stenosis. Whereas community education programs are important, their target guidelines for diet or drug therapy are not as stringent as those for a patient with documented CAD or a genetic predisposition. Therefore, the vigor of risk factor modification should increase with the probability or certainty of having CAD. Vigorous medical reversal therapy should also be considered as an additional step in patients undergoing mechanical intervention to prevent progression of disease that negates the mechanical intervention.

EXERCISE THALLIUM IMAGING AND DIPYRIDAMOLE PET

From Table I, the average sensitivity and specificity of thallium exercise testing in the last 2,877 cases published since 1983 are 83 and 53%, respectively, weighted for

TABLE I Comparison of Thallium Stress Testing and PET

Diagnostic Test	Accuracy (%) Sn	Sp	Patients	Investigators
Diagnosis of coronary artery disease by thallium stress testing since 1963	83	47	197	Van Train et al[32]
	85	52	1,096	Ranhosky and Gerlag[33]
	95	71	210	DePasquale et al[31]
	76	49	832	Schwartz et al[37]
	82	62	461	Iskandrian et al[34]
	94	52	81	Bungo and Leland[38]
Average weighted for no. cases	83	53		
	75	67.5	"corrected"	Diamond[41]
	65	65	"corrected"	Gould[40]
Diagnosis of coronary artery stenosis using ^{82}Rb with a fast PET scanner or $^{13}NH_3$	95	100	50	Gould et al[42]
	94	95	193	Demer et al[44]
	97	100	32	Schelbert et al[45]
	97	100	49	Yonekura et al[46]
	98	93	146	Williams et al[47]
Average weighted for no. cases	96	96		

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$^{13}NH_3$ = radioactive ammonia; PET = positron emission tomography; Rb = rubidium; Sn = sensitivity; Sp = specificity.

number of cases in each study. Sensitivity and specificity of exercise thallium imaging was 80 to 90% in symptomatic patients in the studies published before 1983.[29,30] Studies since 1983 report sensitivity of 70 to 85% and specificity of 45 to 60% in both symptomatic[31–35] and asymptomatic subjects[36,37] or those with atypical presentations,[38] as summarized in Table I. An average specificity of 53% means that there are 47% false-positive thallium exercise tests in patients whose coronary arteriograms show no significant coronary artery stenoses, thereby making the arteriograms unnecessary if a more accurate noninvasive test were used initially.

One proposed explanation for low specificity in recent reports is "referral bias" (i.e., patients with negative thallium stress tests no longer undergo cardiac catheterization).[32,34] The catheterized population in such a study would then be biased by this exclusion of normal subjects, thereby skewing the population toward higher prevalence of disease. According to Bayes' Theorem, as the population is skewed toward greater prevalence of disease, the posttest probability of having no disease with a normal test, and the observed apparent specificity, decrease in that population.[35,36]

However, we have demonstrated that the currently reported low specificity of 50 to 60% is unlikely due to referral bias.[39–41] Accounting for referral bias by a sophisticated model, Diamond[41] estimated an average "corrected" sensitivity of thallium exercise testing of 67.5% and average "corrected" specificity of 75% (Table I). His conclusion agrees with my estimates of 65% sensitivity and 65% specificity, accounting for changing patterns of interpretation but without correction for referral bias.[40] Although referral bias is a valid concept, it cannot be invoked to explain away the poor sensitivity and specificity of thallium exercise testing. Diamond also concluded that SPECT is not superior to planar thallium imaging in diagnostic accuracy and that the use of low-risk groups to establish "normalcy" standards without comparison to coronary arteriography is not correct.

Table I compares currently reported sensitivity and specificity of thallium exercise testing (83 and 53%, respectively) with dipyridamole PET (96 and 96%, respectively).[19,42–50] In a study population with a high prevalence (94%) of severe advanced CAD as reported by Tamaki et al,[51] the differences between PET and thallium SPECT are not apparent[51] because the disease is severe enough to cause high contrast between normal and abnormal areas of images that even limited technology could detect, comparable to a medical history. In addition, at a disease prevalence of 94%, the poor specificity of SPECT is not manifest because there are too few normal subjects or those with less severe disease in the study population. The advantages of advanced PET technology are best observed for intermediate disease prevalence (<60% of the study population) or moderate to less severe CAD where the question of medical or mechanical intervention is unclear and thallium stress testing is least accurate.

In 2 other studies directly comparing PET and SPECT in appropriate populations,[52–54] the diagnostic accuracy of PET was significantly higher than SPECT despite inadequate counts (6 to 7 million counts/whole heart data set) in 1 study[54] and inappropriate PET software in the other,[52,53] as previously analyzed in detail.[19] Using a faster scanner collecting adequate counts (30 to 50 million counts/whole heart data set) and optimized PET software, others have reported higher sensitivity and specificity of ≥95%,[47] comparable to the first major studies from our laboratory.[19,42,44]

ECONOMICS OF POSITRON EMISSION TOMOGRAPHY USING RUBIDIUM-82

Figure 5 shows the comparative diagnostic costs of PET, SPECT or arteriography as a function of disease prevalence.[19,55–57] For this figure, sensitivity and specificity for SPECT and PET were as listed in Table I. The cost of SPECT was $1,000/study, including professional fees, and the cost of PET using generator-produced rubidium-82 was $1,500. Each positive noninvasive test by both technologies was assumed to undergo arteriography costing $6,000. If the cost of coronary arteriography for false-positive tests is counted into the cost of identifying or

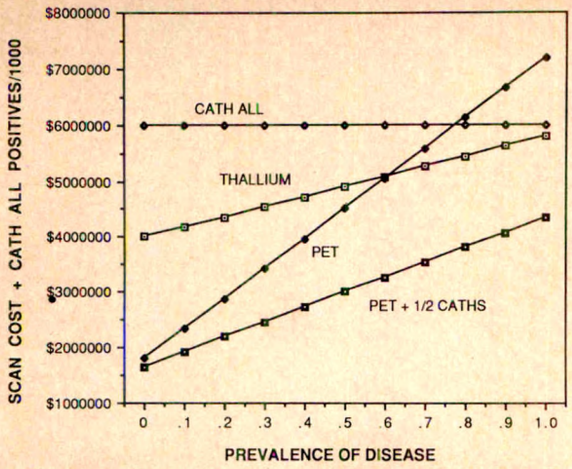


FIGURE 5. Comparative costs of definitive coronary arteriography for false-positive results of the noninvasive tests as a function of disease prevalence. CATH = catheterizaton; PET = positron emission tomography. (Reproduced with permission from *Curr Opinion Cardiol.*[56])

ruling out disease, the overall cost of medical care based on thallium SPECT is higher than for PET due to the higher costs of definitive catheterizations for the false-positive SPECT results.

Since PET also provides an approximate quantitative assessment of severity, it can potentially be used as a substitute for arteriography in many patients with mild-to-moderate disease amenable to medical therapy. If approximately 30 to 40% of patients undergoing coronary arteriography need a mechanical procedure (PTCA or bypass surgery), a large part of the balance of arteriograms not leading to a procedure due to less severe or no disease could be prevented by identifying those patients suitable for medical therapy by PET. As an illustration, this instance is shown by the lower line of Figure 5, where half of the arteriograms in patients who turn out to have mild disease have been eliminated on the basis of PET results showing mild disease. On the other hand, patients with asymptomatic severe disease identified by PET may need mechanical intervention to prevent myocardial infarction or sudden death. Therefore, the use of the rubidium-82 generator instead of a cyclotron for cardiac PET reduces the cost of PET imaging to a reasonable range for routine clinical use as the basis for vigorous medical therapy or mechanical intervention.

In conclusion, traditionally in medicine, the patient and physician wait until angina pectoris, myocardial infarction, arrhythmia, heart failure or sudden death leads to medical or mechanical intervention. However, symptoms are usually late manifestations of advanced disease, when reversal of coronary artery stenosis is difficult and mechanical procedures are often necessary. As a guide to therapy, angina pectoris usually indicates severe coronary artery stenoses, does not predict sudden death or acute myocardial infarction, and can be improved or eliminated by medical therapy without affecting progression of disease. Furthermore, by the time angina pectoris develops, the optimal opportunity for reversal therapy early in the disease has passed. Consequently, diagnosing coronary artery stenosis and its severity at the mildest, earliest possible stage, particularly before symptoms, is important for instituting vigorous risk factor modification.

Although reactive treatment triggered by symptoms appropriately remains central to cardiovascular medicine, advanced diagnostic and therapeutic technology provide the opportunity for another major step in the evolution of cardiovascular medicine. PET has sufficient diagnostic power for a new therapeutic approach based on routine, economical, noninvasive diagnosis and assessment of severity in symptomatic or asymptomatic patients with intense dietary or medical treatment for reversal of CAD. Such therapy may not be appropriate for the general population or for patients without known coronary artery stenosis. It is therefore targeted, individual specific, preventive intervention. For severe silent disease identified by PET, coronary arteriography and mechanical intervention may be indicated to prevent myocardial infarction or sudden death.

In contrast with the traditional approach based on symptoms, this new approach is based on functional and anatomic characterization of stenoses and myocardial viability, with sufficient reliability in symptomatic or asymptomatic patients to justify medical or mechanical interventions having significant benefits and risks, or to avoid unnecessary interventions. The scientific basis for this approach has been documented and the feasibility has been demonstrated.[19]

The central issue is whether society wants to find existing CAD and treat it. Currently, we have the knowledge and the technology for noninvasively finding (or excluding) and treating symptomatic or asymptomatic CAD by medical or mechanical intervention. The population at risk for coronary atherosclerosis is sympathetic to this view because sudden death and myocardial infarction are so common. Those who deliver cardiovascular care are willing to provide these services based on high quality medical practice, professionalism and economic incentive. Opponents of this view cite the cost of PET as a major problem. However, economic analysis of cardiac PET using rubidium-82 for symptomatic or asymptomatic subjects with coronary atherosclerosis demonstrates that it is less expensive than the cost of definitive coronary arteriography now performed in many normal patients with false-positive thallium stress tests.[19]

PET technology is now available and has proven effective as well as economical in multiple private practice sites for routine, high-volume cardiac diagnosis and management. It is important that in >3,000 cardiac PET studies at private sites, virtually all private health insurers reimburse fully for cardiac PET with rubidium-82 because it is approved by the Food and Drug Administration and because the insurers realize that it prevents many unnecessary coronary arteriograms and mechanical interventions while correctly identifying those patients for whom such procedures are essential even if they

are asymptomatic. Selective specific medical intervention to reverse coronary atherosclerosis or selective mechanical intervention for severe disease to prevent myocardial infarction or sudden death are not only good medicine but also cost effective.

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Role of Magnetic Resonance Contrast Agents in Cardiac Imaging

Gerald L. Wolf, PhD,MD

Improvements in magnetic resonance imaging (MRI) technology allow adequate spatial and temporal resolution to capture cardiac anatomy and contractile function in exceptional detail and with little risk. However, tissue characterization of the pathophysiologic state of the myocardium may require special indicators or MR contrast agents. These must be tailored for detection by the MRI process, but available agents are effective at low dose and provide a wide range of indicator properties (e.g., myocardial extracellular space, blood pool, capillary permeability and membrane transport). Each agent has a dynamic washin and washout time-intensity curve that may reflect myocardial perfusion or consequences of ischemia. The combined use of MRI and MR contrast agents may provide a single diagnostic examination that fully and quantitatively assesses all indexes of cardiac performance. Such information would be both global and regional, and would be well tolerated by patients. The cost, value and cost-effectiveness of such studies remain speculative.

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Magnetic resonance (MR) technology is still rapidly evolving. Early investigators believed that MR imaging (MRI) would always be slow and would never require contrast agents. However, research laboratories are working with new clinical MR instruments that have exceptional spatial and temporal resolution, flexible selection of 2, 3 or more dimensions, and extraordinary contrast choices. The number of patients imaged is now in the millions with little evidence of untoward events save those related to improper technique. Concerns about biohazard from electromagnetic fields is directed to lower frequency windows [60 Hz] than used for MR imaging.

Unenhanced MRI provides accurate depiction of the myocardial wall, chambers and great vessels, as reviewed by Peshock[1] in this symposium. The wide field of view and optional plane of imaging are especially useful for cardiac imaging.

Motion is both a problem and an opportunity with unenhanced MRI. Myocardial contraction, valvular function and the complicated effects of pulsatile blood flow and turbulence are addressable with special techniques and a sophisticated interpreter.[2–4] However, detecting and measuring regional myocardial pathology or perfusion is not yet possible with unenhanced MRI.

TISSUE RELAXATION AND MYOCARDIAL MAGNETIC RESONANCE SIGNAL

The relations between signal intensity, instrument parameters, myocardial spin density, spin-lattice relaxation time (T1) and spin-spin relaxation (T2) are fairly well understood but complex.[5] The formal equation ("MR algebra") always includes a motion term that is conveniently ignored—but at peril of significant misunderstanding. Cardiac motion includes respiration, contraction and macroscopic as well as microscopic perfusion. The impact of this motion on MR signal varies significantly with all imaging parameters, including pulse sequences, method of signal detection, plane, slice thickness, angle relative to the motion, in-plane and out-of-plane saturation, and with parameters of the biologic motion, including direction, magnitude, number of moving spins, velocity, acceleration, and real or apparent proton relaxation.

Myocardial ischemia can change many of these determinants of MR signal intensity and in complex and often opposite ways. Table I lists a qualitative summary of the likely effect of many ischemic consequences on the net or summed MR signal. Ischemia is also an evolutionary process with many temporal and anatomic determinants. Motion effects, though poorly understood, are the earliest and most sensitive indices. Edema, necrosis and healing

TABLE I Summary of Expected Changes in Cardiac Images by Stage of Myocardial Ischemia

	Myocardial Cells	Perfusion	Contractility	Net Imaging Effect
Reversible ischemia	1. mild swelling p↑, T2↑	1. decreased T2↑ 2. Deoxy Hb T2↓	1. decreased T2↑ S/N↑	I slightly ↑
Irreversible	1. more swelling p↑↑, T1↑, T2↑↑ 2. molecular breakdown and release T1↓, T2↓		1. absent T1↑ S/N↑	I↑↑
Reperfusion	1. explosive cell swelling p↑↑↑, T1↑, T2↑↑↑	1. hypo-perfusion T2↑ 2. hyper-perfusion T2↓	1. variable	I↑↑↑
Repair early	1. granulation tissue p↑, T1↑ T2 sl↑	1. subacute hemorrhage T1↓↓, T2↓	1. hypokinetic	I↑
Late	1. scar p↓, T1 sl↓ T2↓	1. ± hemosiderin T2↓↓		I↓

Deoxy Hb = deoxyhemaglobin; I = image density; p = proton density; S/N = signal-noise ratio; T1 = spin-lattice relaxation time; T2 = spin-spin relaxation; ↑ = increased; ↓ = decreased.

all change myocardial proton relaxation, but on a much slower time scale. This is of particular concern for interventions.

MAGNETIC RESONANCE CONTRAST AGENTS FOR THE HEART

When a measurement is complex or difficult, it is often easier to measure accurately a change in value than to measure accurately the absolute value. To the extent that the agent causing the change is better understood than the undisturbed process, the measurements are also easier to interpret and use (i.e., have more value).

TABLE II Potential Indicators (Magnetic Resonance Contrast Agents) for Cardiac Imaging

Extracellular agents	
GdDTPA	GdBMA (SO4I)
GdDOTA	DyDTPA
Nitroxides (TES, etc.)	
Blood pool agents	
GdDTPA-albumin	
GdDTPA polysaccharides	
Magnetite particles	
Intracellular agents	
$MnCl_2$	Gd-PMP
Mn-TP	MnPDTA
Mn-DPDP	

DTPA = diethylene triamine pentaacetic acid; Dy = dysprosium; Gd = gadopentatate dimeglumine; GdBMA = GdDTPA his methylamide; GdDOTA = polyazo macrocyclic ligand; Gd-PMP = polymethyl phosphate; Mn-DPDP = manganese dipyridoxal ethylene diamine diacetate phosphate; MnPDTA = propylamine diamine pentaacetic acid; Mn-TP = tetraphosphate; $MnCl_2$ = manganese dichloride.

Fortunately, scientists have often used an indicator with known properties to measure an otherwise unavailable process, and the principles of indicator-dilution are familiar. For imaging applications, such exogenous indicators are called contrast agents. The good news is that 2 classes of such agents are available for MR detection and the detectable amounts are orders of magnitude smaller than iodine-based indicators imaged with x-ray methods (Table II). This detection advantage can be used to make more safe compounds, provide a wider variety of indicator distributions or improve cost-effectiveness.

For example, MR contrast agents are available to follow distribution and equilibration in the extracellular space, the blood pool, the monocyte-macrophage pool and the myocardial intracellular space (Table III).[6,7] Some of the latter appear to be sensitive to ischemia or myocardial metabolism. Many appear safe enough to be given as a bolus or infusion, resulting in measurable changes in the MR images of the heart. The bad news is that the MR signal changes are somewhat complex.

MR imaging is designed to be sensitive to proton relaxation, but protons have only 2 energy states in magnetic fields. Thus, all relaxation processes have the same effect on the image. Further, MR contrast agents are not directly visualized; only their effects on relaxation are recorded. So the added relaxation of the MR indicator or contrast agent is summed with inherent relaxation. The final confounder is that there are 2 proton relaxations, T1 and T2, that affect the image intensity in different and usually opposite fashion. The complexities that follow are

TABLE III Magnetic Resonance Imaging Contrast Agents

	Paramagnetic Chelate	Superparamagnetic Particles	Ferromagnetic Particles
T1	↓		
T2	↓	↓↓↓	↓↓↓↓
Physical form	Chelates dissolved in solution	Fe aggregates as small particles	Fe aggregates as large particles
No. of paramagnetic atoms/molecule	1	10^{10}	10^{12}
Examples	Iron EDTA Manganese EDTA Gadolinium DTPA	Dextran plus magnetite	Microspheres plus magnetite

EDTA = ethylene diamine tetraacetic acid; Fe = iron; Other abbreviations as in Tables I and II.

reviewed elsewhere.[7–9] The rapid recirculation of indicators in the myocardial bed puts further limits on intravenous bolus schemes for quantitating regional indicator dilution.

All of these issues seem tractable, and current dynamic MR studies of myocardial washin and washout of MR contrast agents are visually appealing and seem capable, at a minimum, of providing relative myocardial pathophysiology measures at an anatomic resolution of <1 ml of tissue.

Substantial opportunities remain for development of new contrast agents and for new uses of established agents. We have tended to separate MR contrast agents into 2 classes—paramagnetic chelates and superparamagnetic particles—as listed in Table II. It is evident that there is a huge opportunity to explore the gap between these 2 extremes of 1 active paramagnet/molecule and 10^{10} ferrimagnetic molecules/particle when they are juxtaposed as in Table II. This gap has begun to narrow in both directions. Thus, Schmiedl and co-workers[10] are among the leaders in placing several gadolinium atoms on a single large molecule (albumin with a molecular size of 1 to 3 nM). This class of MR contrast agents reports local perfusion during the early washin phase, local myocardial capillary permeability in the accumulation phase, and relative blood volume or leak space in the static phase. With carefully selected imaging schemes, animal models show good detection of myocardial ischemia.

Narrowing the gap from the other direction, Weissleder and co-workers[11] have prepared ultrasmall superparamagnetic iron oxide particles with a mean diameter of 11 nM. The smaller particles are not as rapidly cleared by phagocytes and blood life is increased. When attached to receptor molecules, this longer blood life has provided selective imaging of liver cell membrane receptors and may allow other cell surface macromolecules to be noninvasively imaged.

All MR contrast agents that are compartmentalized by their biodistribution will generate a magnetic susceptibility gradient within tissue. Gradient echo imaging schemes are available on most clinical magnets and this assures good detectability of such effects. Thus, the blood brain barrier restricts gadopentatate dimeglumine diethylene triamine pentaacetic acid and dysprosium diethylene triamine pentaacetic acid to brain capillaries, and qualitative brain perfusion is reflected in dynamic MRI studies. The cell membrane also excludes these 2 agents, creating a compartmentalization that also allows visualization of washin and washout kinetics for these indicators in substantially all tissues. Agents restricted to the blood pool are better compartmented in vital organs such as heart, kidney and liver. All such agents are capable of demonstrating local perfusion or other local function. The exquisite geographic resolution of MRI reduces the averaging artifacts that result when measuring in vivo function from plasma disappearance curves. In many cases, the MR indicator is eliminated or equilibrates in reasonable time periods so that the efficacy of a medical intervention can be studied using repeat examinations.

Manganese preparations continue to be of interest but are difficult to use with safety.[12,13] Many organs are avid for manganese and appear to acquire it from most available chelators. Manganese has important intracellular activities and can be toxic. On the other hand, only manganese is readily eliminated by homeostatic systems—a property not shared by free iron or gadolinium. Clearly, intracellular targeting is more hazardous, but possibly more informative than other indicators.

Early studies with radiomanganese suggested that cellular uptake depended on membrane transport and energy.[14,15] Ischemic myocardium is less efficient in accumulating manganese and the relation may be sensitive to blood flow. Manganese is less readily expelled from normal myocardium and there may be little redistribution. Such behavior would make safe manganese contrast agents easier to use in stress testing circumstances that are inconvenient or unsafe to perform within the imaging magnet.

There is interest in developing MR contrast agents sensitive to excess local calcium. If feasible, such agents would provide the biodistribution of pyrophosphate radioactive preparations with the much better imaging capabilities of MRI.

Costs remain relatively high but there appear to be major opportunities to increase value. Even without providing the equivalent of coronary angiography, a single contrast-enhanced MR examination that quantitatively evaluated cardiac anatomy, function and myocardial per-

fusion would be cost-effective. Such an examination would reduce the use of ultrasound, nuclide scanning and cine computed tomography and could relegate coronary angiography to a setting where an interventional procedure was also likely to be performed at the same time.

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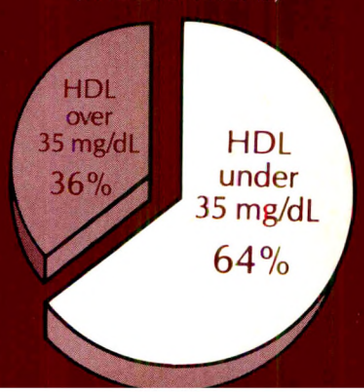
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CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

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3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy** – Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy** – Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions** – (A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility** – Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B** – Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers** – Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes** – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function** – Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children** – Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

References: 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-1245. 2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651. 3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J. B. et al. (eds.): *The Metabolic Basis of Inherited Disease*, 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642.

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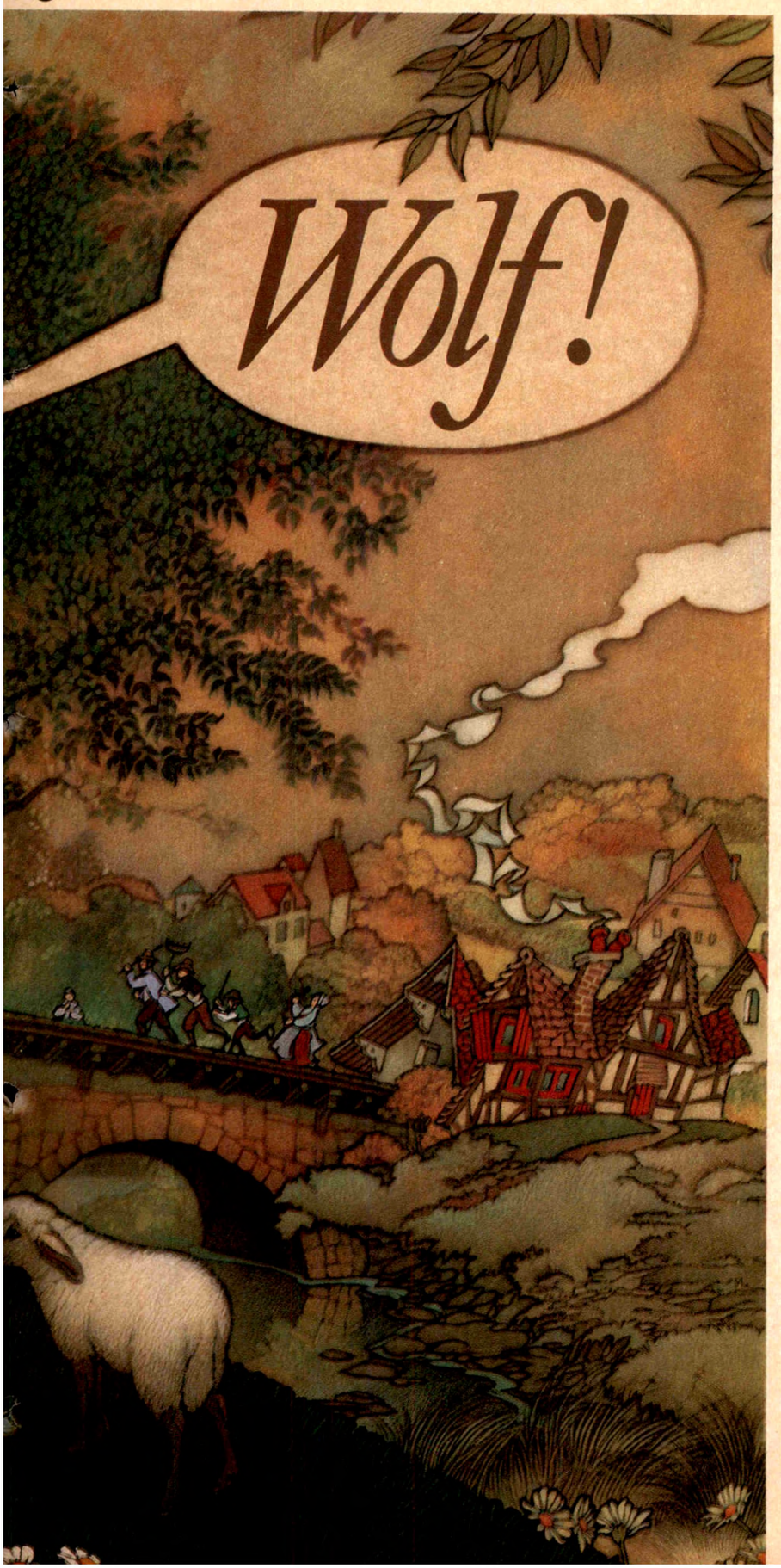
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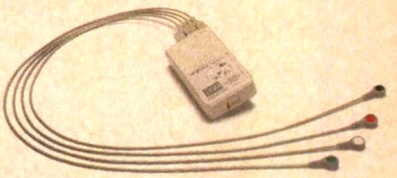
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CORONARY ARTERY DISEASE

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Frank Litvack, Neal L. Eigler, James R. Margolis, Warren S. Grundfest, Donald Rothbaum, Thomas Linnemeier, Lisa B. Hestrin, Daniel Tsoi, Stephen L. Cook, Daniel Krauthamer, Tsvi Goldenberg, James R. Laudenslager, Jacob Segalowitz, and James S. Forrester

Unlike balloon angioplasty, which can stretch the arterial wall, displacing or bypassing an atheroma, the pulsed excimer laser can ablate even calcified tissue with minimal thermal injury. In this ongoing study of the first 55 patients ever to undergo percutaneous excimer laser coronary angioplasty, the success rate thus far is 84% and there have been no cases of vascular perforation or of death.

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Results of Percutaneous Transluminal Coronary Angioplasty in Patients ≥65 Years of Age (from the 1985 to 1986 National Heart, Lung, and Blood Institute's Coronary Angioplasty Registry)
Sheryl F. Kelsey, David P. Miller, Richard Holubkov, Ann S. Lu, Michael J. Cowley, David P. Faxon, Katherine M. Detre, and Investigators from the NHLBI PTCA Registry

The 1985 to 1986 NHLBI Percutaneous Transluminal Coronary Angioplasty Registry series of 1,801 initial patients included 486 patients ≥65 years (elderly). At 2-year follow-up, all-cause mortality was higher among elderly patients, but elderly patients had no more myocardial infarction, coronary artery bypass grafting, repeat PTCA or angina than younger patients.

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Benno J. Rensing, Walter R.M. Hermans, Kevin J. Beatt, Gert Jan Laarman, Harry Suryapranata, Marcel van den Brand, Pim J. de Feyter, and Patrick W. Serruys

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Timing and Mechanism of In-Hospital and Late Death After Primary Coronary Angioplasty During Acute Myocardial Infarction
Joel K. Kahn, James H. O'Keefe, Jr., Barry D. Rutherford, David R. McConahay, Warren L. Johnson, Lee V. Giorgi, Thomas M. Shimshak, Robert W. Ligon, and Geoffrey O. Hartzler

We determined the mechanism and timing of in-hospital and late deaths among a group of 614 patients treated with primary infarct angioplasty without antecedent thrombolytic therapy. Death after primary infarct angioplasty is related to the status of the left ventricle and the extent of coronary artery disease.

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Circadian Rhythm of Heart Rate Variability After Acute Myocardial Infarction and Its Influence on the Prognostic Value of Heart Rate Variability
Marek Malik, Thomas Farrell, and A. John Camm

What is the best interval of day to record the heart rates of patients after an acute myocardial infarction when trying to predict their risk of sudden cardiac death or serious arrhythmic events, or both? Herein, the electrocardiograms of 2 matched groups of 20 patients, recorded during the first 2 weeks after AMI, are analyzed and compared with respect to heart rate and heart rate variability during the course of a day.

1055
Doppler Assessment of Left Ventricular Filling Pattern in Silent Ischemia in Patients with Prinzmetal's Angina
Elisabetta Doria, Piergiuseppe Agostoni, Alessandro Loaldi, and Cesare Fiorentini

Left ventricular diastolic function during 16 episodes of spontaneous angina pectoris was studied by simultaneous recordings of electrocardiographic, echocardiographic and hemodynamic parameters in 6 patients with Prinzmetal's angina. Three distinct phases (waxing, steady and waning) were demonstrated. Transmitral Doppler flow tracings in each phase showed significant changes only in early diastole.

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Aortic Calcified Plaques and Cardiovascular Disease (The Framingham Study)
Jacqueline C. M. Witteman, William B. Kannel, Philip A. Wolf, Diederick E. Grobbee, Albert Hofman, Ralph B. D'Agostino, and Janet C. Cobb

The relation between the presence of calcified plaques in the thoracic aorta and subsequent cardiovascular disease is examined during 12 years of follow-up of the Framingham cohort (n = 5,209). Presence of aortic calcified plaques was associated with a twofold increase in risk of cardiovascular death in men and women aged <65 years. Aortic calcified plaques detected on a chest x-ray in a relatively young person indicates an increased risk of cardiovascular disease.

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Comparison of Direct and Indirect Measures of Systemic Arterial Pressure During Weightlifting in Coronary Artery Disease
Elizabeth M. Wiecek, Neil McCartney, and Robert S. McKelvie

Direct and indirect measures of arterial pressure during weightlifting in 5 men with coronary artery disease were compared. Indirect estimates of systolic pressure are significantly less than arterial values at rest, and during and after lifting. Because of the rapid decrease in pressure that occurs after exercise, indirect measurements after lifting do not allow accurate conclusions to be drawn about arterial pressures generated during lifting.

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Response of Angiographically Normal and Atherosclerotic Left Anterior Descending Coronary Arteries to Acetylcholine

Christopher M. Newman, Attilio Maseri, David R. Hackett, Hassan M. El-Tamimi, and Graham J. Davies

We examined the sequential segments of left anterior descending coronary arteries, angiographically normal in 10 patients and atherosclerotic in 7, after infusions of increasingly concentrated doses of intracoronary acetylcholine. Our results call into question the concept that a constrictor response to intracoronary acetylcholine necessarily indicates the presence of coronary atherosclerosis.

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Intraoperative Myocardial Contrast Echocardiography for Assessment of Regional Bypass Perfusion

Harald Mudra, Werner Zwehl, Volker Klauss, Eckart Kreuzer, Mathias C. Haufe, Christiane Angermann, and Karl Theisen

Sonicated iopromid (2 ml, microbubble size 6 ± 4 μm) was injected into 11 grafts during routine coronary bypass surgery. Myocardial contrast echocardiography is a safe, feasible method for evaluating coronary bypass grafts intraoperatively.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

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Clinical and Electrophysiologic Characteristics of Patients with Antidromic Circus Movement Tachycardia in the Wolff-Parkinson-White Syndrome

Jacob Atié, Pedro Brugada, Josep Brugada, Joep L.R.M. Smeets, Fernando E.S. Cruz, Ayrton Peres, Marie P. Roukens, and Hein J.J. Wellens

In 36 of 345 consecutive patients, 56 distinct antidromic tachycardias were recorded and several different pathways observed. Multiple accessory pathways were identified in 12 of the 36 patients. Four patients were resuscitated from ventricular fibrillation.

1092

Persistence of Arrhythmia Exercise Response in Healthy Young Men

Yaacov Drory, Amos Pines, Enrique Z. Fisman, and Jan J. Kellermann

The scarce data available on exercise-induced arrhythmia in young healthy adults prompted this long-term (mean 6.7 years) follow-up evaluation of 76 men (mean age 21.5 years) who presented with arrhythmias at rest, during exercise, or both. Further studies may be needed for long-term prognoses, but results suggest that arrhythmias without underlying heart disease reflect a benign natural history in these young men at this time.

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Electrocardiographic Signal-Averaging During Atrial Pacing and Effect of Cycle Length on the Terminal QRS in Patients With and Without Inducible Ventricular Tachycardia

Mark S. Kremers, William H. Black, Richard Lange, Peter J. Wells, and Martha Solo

To determine the effect of heart rate on late potentials in 15 patients without and 7 patients with inducible sustained ventricular tachycardia, we performed electrocardiographic signal-averaging during sinus rhythm and atrial pacing. At rates from 61 to 171 beats/min, the signal-averaged electrocardiogram is largely independent of heart rate, but there is a trend toward a decrease in terminal voltage and an increase in low-amplitude terminal QRS duration in patients with inducible VT.

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Reproducibility in Circadian Rhythm of Ventricular Premature Complexes

Gaetano A. Lanza, Maria C. Cortellessa, Antonio G. Rebuzzi, Enrico V. Scabbia, Alessandra Costalunga, Sergio Tamburi, Michele Lucente, and Ugo Manzoli

Can antiarrhythmic medications be synchronized with the acrophases of ventricular premature complexes? To pinpoint the existence and reproducibility of circadian rhythms of VPCs, we monitored 19 patients with coronary artery disease and 19 people with structurally normal hearts for 2 days and found a significant circadian trend in patients with VPCs.

CONGESTIVE HEART FAILURE

1107

Comparison of Intravenous Amrinone and Dobutamine in Congestive Heart Failure Due to Idiopathic Dilated Cardiomyopathy

Richard H. Marcus, Keith Raw, Jay Patel, Abdul Mitha, and Pinhas Sareli

Hemodynamic responses to infusions of amrinone or dobutamine were compared in 46 patients with dilated cardiomyopathy in heart failure unresponsive to oral medication. Advantages of amrinone were a higher individualized response rate, a more consistent diuretic effect and a more predictable effective dose; however, this agent also caused a tachycardia, which was not observed with dobutamine.

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Comparison of Frequency of Late Potentials in Idiopathic Dilated Cardiomyopathy and Ischemic Cardiomyopathy with Advanced Congestive Heart Failure and Their Usefulness in Predicting Sudden Death

Holly R. Middlekauff, William G. Stevenson, Mary A. Woo, Debra K. Moser, and Lynne Warner Stevenson

Signal-averaged electrocardiograms were obtained in 62 consecutive patients with advanced congestive heart failure. The signal-averaged electrocardiogram and ambulatory electrocardiogram provide independent information for possible risk assessment in CHF; however, late potentials are poor predictors of sudden death risk when CHF is advanced, possibly due to the heterogeneity of causes of sudden death.

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Value of Carvedilol in Congestive Heart Failure Secondary to Coronary Artery Disease
Prabir Das Gupta, Paul Broadhurst, Edward B. Raftery, and Avijit Lahiri

A new β-blocking agent with vasodilating properties, carvedilol, was evaluated in 17 patients with chronic congestive heart failure secondary to coronary artery disease. Results showed significant increases in exercise capacity, resting ejection fraction and stroke volume index, along with reductions in pulmonary artery wedge pressure, systemic vascular resistance, and rest and exercise heart rate and blood pressure.

VALVULAR HEART DISEASE

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Improvement in Early Diastolic Filling Dynamics After Aortic Valve Replacement
Ian C. Gilchrist, Harvey L. Waxman, and Peter B. Kurnik

Using ultrafast computed tomography, we evaluated the relation between left ventricular mass and diastolic function in 13 patients undergoing aortic valve replacement for aortic stenosis. Improvement in diastolic function was seen after aortic valve surgery and was associated with improved functional class. Changes in diastolic function occurred after regression in wall mass, suggesting a delayed remodeling of the ventricle.

MISCELLANEOUS

1131
Lipoprotein and Hepatic Lipase Activity and High-Density Lipoprotein Subclasses After Cardiac Transplantation
H. Robert Superko, William L. Haskell, and Connie D. Di Ricco

How do immunosuppressive medications—cyclosporine, azathioprine and prednisone—interact with serum lipids and lipoprotein metabolism? To learn if these medications could help reduce the risk of graft atherosclerosis, we compared metabolic values in 72 consecutive cardiac transplant patients with those in 51 healthy control subjects.

1135
Serial Evaluation of Lipid Profiles and Risk Factors for Development of Hyperlipidemia After Cardiac Transplantation
Laszlo Rudas, Peter W. Pflugfelder, F. Neil McKenzie, Alan H. Menkis, Richard J. Novick, and William J. Kostuk

Eighty-three consecutive 1-year survivors of heart transplantation were studied to determine prevalence, time course and factors responsible for hyperlipidemia. Elevated serum total cholesterol and triglyceride levels were noted in patients with a pretransplant diagnosis of coronary artery disease and obesity.

EDITORIAL

1139
Late Proarrhythmia and Understanding the Time of Occurrence of Proarrhythmia
Harold L. Kennedy

BRIEF REPORTS

1144
Electrocardiographic Q-Wave Inconstancy in Inferior Wall Myocardial Infarction
Mei-Yu Chuang and David H. Spodick

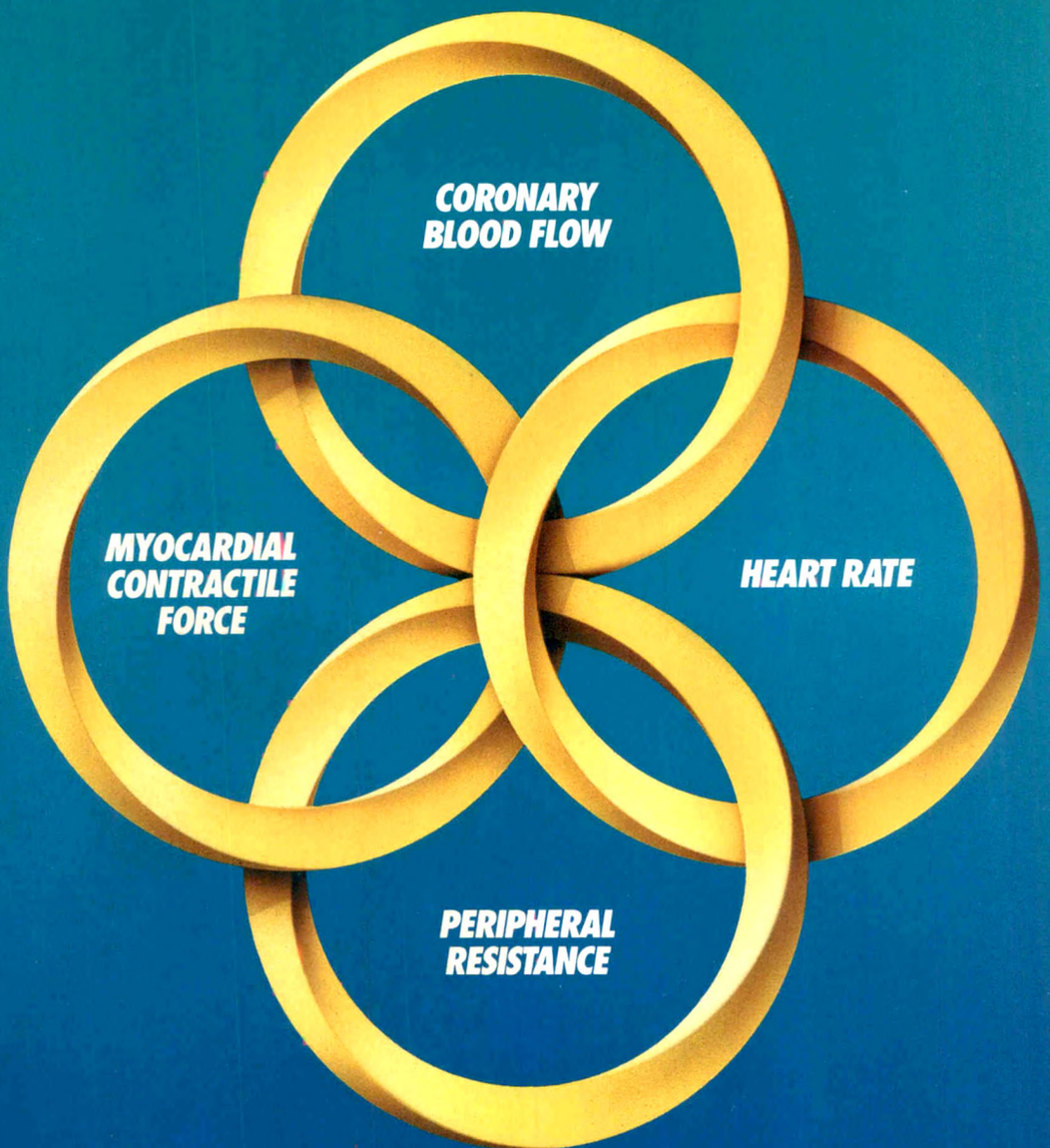
1146
ST Elevation in the Right Chest Leads in Anterior Wall Left Ventricular Acute Myocardial Infarction
Hajime Kataoka, Akira Tamura, Shoji Yano, Koreyasu Kanzaki, and Yoshiaki Mikuriya

1147
Emergency Stenting for Refractory Acute Coronary Artery Occlusion During Coronary Angioplasty
Pim J. de Feyter, Ivan DeScheerder, Marcel van den Brand, GertJan Laarman, Harry Suryapranata, and Patrick W. Serruys

INSTRUCTIONS TO AUTHORS on page 1130

CLASSIFIED ADVERTISING on pages A58, A64, A67

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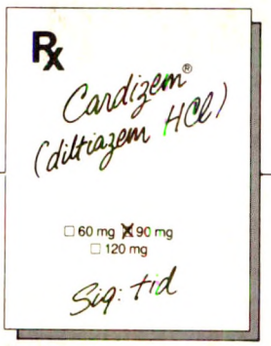


diltiazem HCl TABLETS

CARDIZEM (diltiazem HCl) is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

Please see brief summary of prescribing information on next page.

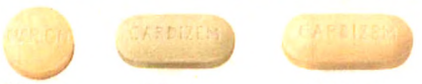
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Usual maintenance dosage:
180 to 360 mg/day

CARDIZEM® TABLETS
diltiazem HCl

MAKING THE DIFFERENCE IN ANGINA



60 mg 90 mg 120 mg

BRIEF SUMMARY

CARDIZEM®
(diltiazem HCl) Tablets

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes, however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)

Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular: Angina, arrhythmia, AV block (first degree), AV block (second or third degree — see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope.

Nervous System: Amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase.

Dermatologic: Petechiae, pruritus, photosensitivity, urticaria.

Other: Amblyopia, CPK elevation, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

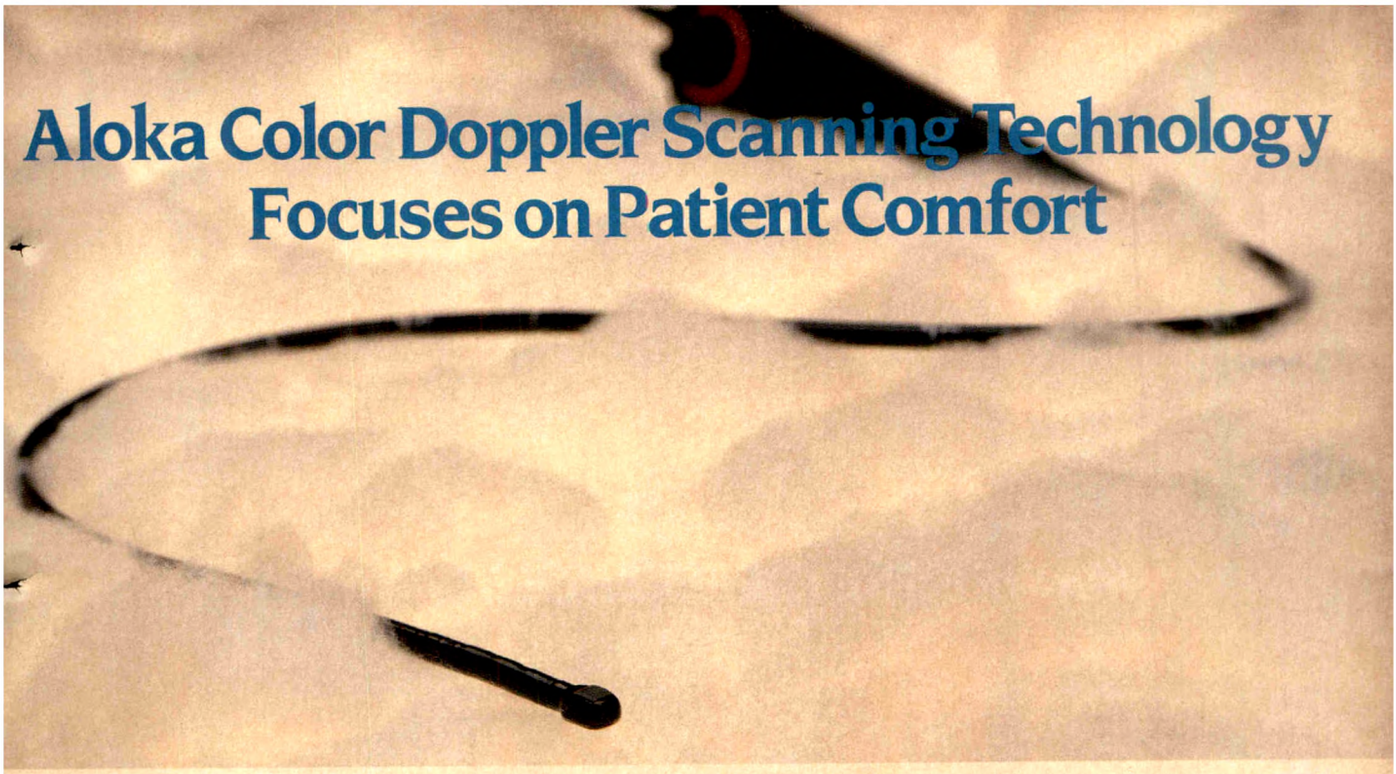
The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

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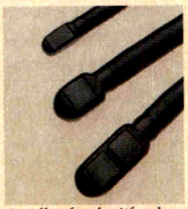
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Patient comfort and diagnostic precision now come in three probe varieties. Because these probes are so easy to swallow, they greatly broaden the range of ultrasound applications.

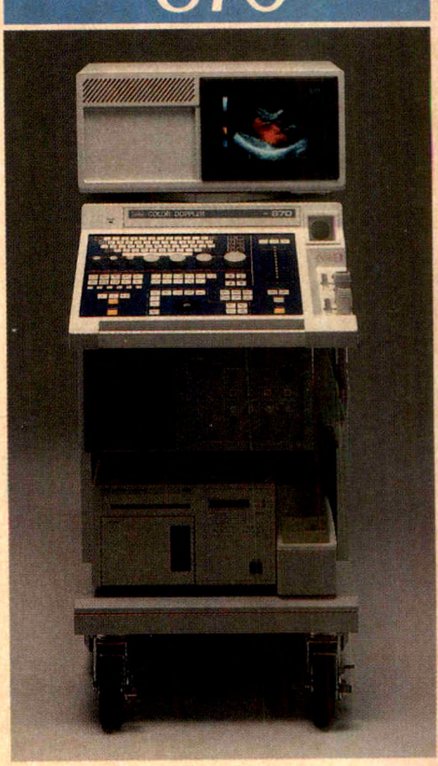
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The American Journal of Cardiology

NOVEMBER 1, 1990, VOL. 66, NO. 15

CORONARY ARTERY DISEASE

1027
Percutaneous Excimer Laser Coronary Angioplasty

Frank Litvack, Neal L. Eigler, James R. Margolis, Warren S. Grundfest, Donald Rothbaum, Thomas Linnemeier, Lisa B. Hestrin, Daniel Tsoi, Stephen L. Cook, Daniel Krauthamer, Tsvi Goldenberg, James R. Laudenslager, Jacob Segalowitz, and James S. Forrester

To determine the efficacy of percutaneous excimer laser coronary angioplasty as an adjunct or alternative to conventional balloon angioplasty, 55 patients studied in a multicenter trial underwent the procedure using a modification of the conventional balloon angioplasty technique. Acute success was achieved in 46 of 55 (84%) patients. There were no deaths and no vascular perforations. One patient required emergency coronary bypass surgery. These data suggest that excimer laser energy delivered percutaneously by specially constructed catheters can safely ablate atheroma and reduce coronary stenoses. As experience is gained with larger diameter catheters that minimize the need for adjunctive balloon angioplasty, the procedure may represent an alternative to balloon angioplasty.

1033
Results of Percutaneous Transluminal Coronary Angioplasty in Patients ≥65 Years of Age (from the 1985 to 1986 National Heart, Lung, and Blood Institute's Coronary Angioplasty Registry)

Sheryl F. Kelsey, David P. Miller, Richard Holubkov, Ann S. Lu, Michael J. Cowley, David P. Faxon, Katherine M. Detre, and Investigators from the NHLBI PTCA Registry

The 1985 to 1986 National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty (PTCA) Registry series of 1,801 initial procedures included 486 patients aged ≥65 years (elderly). In comparison to younger patients, among the elderly there were more women and more patients with a history of hypertension, a history of congestive heart failure, unstable angina and more extensive vessel disease. Angiographic success rates were similar for all age groups. Elderly patients were much more likely to require emergency coronary artery bypass graft surgery (CABG) (5.4 vs 2.8%, $p < 0.05$) or elective CABG (3.9 vs 1.6%, $p < 0.01$). The in-hospital death rate of elderly patients was considerably higher (3.1 vs 0.2%, $p < 0.01$). At 2-year follow-up, all-cause mortality was higher among elderly patients (8.8% of patients ≥65 vs 2.9% of

Continued on page A16



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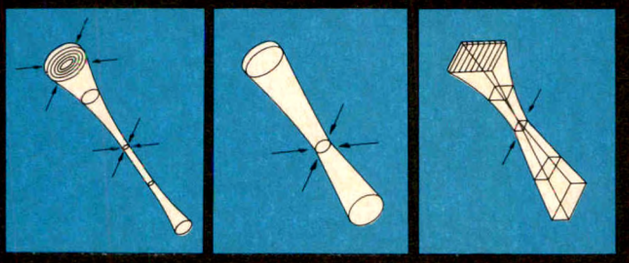
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patients <65 years, p <0.01), but elderly patients had no more myocardial infarction, CABG, repeat PTCA or angina than younger patients.

1039

Quantitative Angiographic Assessment of Elastic Recoil After Percutaneous Transluminal Coronary Angioplasty

Benno J. Rensing, Walter R.M. Hermans, Kevin J. Beatt, Gert Jan Laarman, Harry Suryapranata, Marcel van den Brand, Pim J. de Feyter, and Patrick W. Serruys

Little is known about the elastic behavior of the coronary vessel wall directly after percutaneous transluminal coronary angioplasty (PTCA). Minimal luminal cross-sectional areas of 151 successfully dilated lesions were studied in 136 patients directly after withdrawal of the balloon. Elastic recoil was defined as the difference between balloon cross-sectional area of the largest balloon used at the highest inflation pressure and the minimal cross-sectional area directly after PTCA. Mean balloon cross-sectional area was 5.2 ± 1.6 mm^2 and mean minimal cross-sectional area after PTCA was 2.8 ± 1.4 mm^2. This means a nearly 50% loss of the theoretically achievable cross-sectional area (i.e., balloon cross-sectional area). Oversizing of the balloon (balloon artery ratio >1) led to more recoil (0.8 vs 0.6 mm, p <0.001), suggestive of an elastic phenomenon. A statistically significant difference in recoil was also observed in the 3 coronary arteries.

1045

Timing and Mechanism of In-Hospital and Late Death After Primary Coronary Angioplasty During Acute Myocardial Infarction

Joel K. Kahn, James H. O'Keefe, Jr., Barry D. Rutherford, David R. McConahay, Warren L. Johnson, Lee V. Giorgi, Thomas M. Shimshak, Robert W. Ligon, and Geoffrey O. Hartzler

The mechanism and timing of in-hospital and late deaths among a group of 614 patients treated with primary infarct angioplasty without antecedent thrombolytic therapy were determined. Death occurred in 49 patients (8%) before hospital discharge. Death was due to cardiogenic shock in 22 patients, acute vessel reclosure in 5 patients, was sudden in 8 patients and followed elective coronary artery bypass surgery in 8 patients. Cardiac rupture was observed in only 2 patients after failed infarct angioplasty. During a follow-up period of 32 ± 21 months (range 1 to 87), 55 patients died. The cause of death was cardiac in 36 patients, including an arrhythmic death in 23 patients, and was due to circulatory failure in 13 others. Actuarial survival curves demonstrated overall survival after hospital discharge of 95 and 87% at 1 and 4 years, respectively. Multivariate predictors of late death included 3-vessel disease, a baseline ejection fraction of ≤40%, age >70 years and female gender. Thus, death after primary infarct angioplasty is related to the status of the left ventricle and the extent of coronary artery disease.

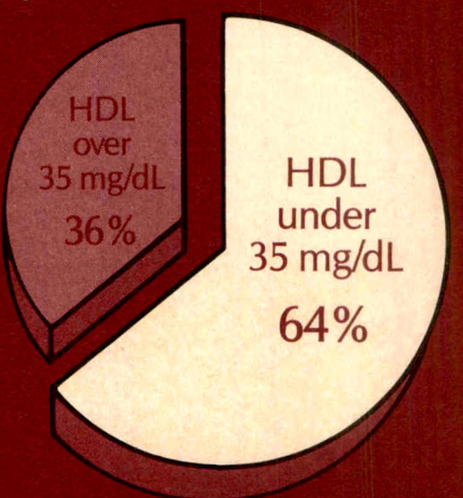
Continued on page A23

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What's a common denominator of most heart attack victims?

Mixed hyperlipidemias—elevated cholesterol *and* triglycerides—are common among heart attack victims,[1] and nearly two thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.[2]



HEART ATTACK PATIENTS (PROCAM TRIAL)[2]

LOPID raised low HDL 25%

—in patients whose baseline HDL was below 35 mg/dL in the landmark Helsinki Heart Study (HHS).[3]

Reduced heart attack incidence* up to 62%

—in these HHS patients and 45% in HHS patients whose baseline HDL was below the median (46.4 mg/dL). Incidence of serious coronary events was similar for LOPID and placebo subgroups with baseline HDL above the median (46.4 mg/dL).[3]

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LOPID is indicated for reducing the risk of coronary heart disease (CHD) in Type IIb patients with low HDL, in addition to elevated LDL and triglycerides, and who have had an inadequate response to weight loss, diet, exercise, and other pharmacologic agents such as bile acid sequestrants and nicotinic acid.

*Defined as a combination of definite coronary death and/or definite myocardial infarction.

References: 1. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. *J Clin Invest.* 1973;52:1533-1543. **2.** Assmann G, Schulte H. *PROCAM-Trial: Prospective Cardiovascular Münster Trial.* Zürich: Panscientia Verlag; 1986:8-9. **3.** Data on file, Medical Affairs Dept, Parke-Davis.

Please see adjacent page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

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Lopid® (Gemfibrozil Capsules and Tablets)

Before prescribing, please see full prescribing information.
A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts—Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy**—Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy**—Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions**—(A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility**—Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

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from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children**—Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

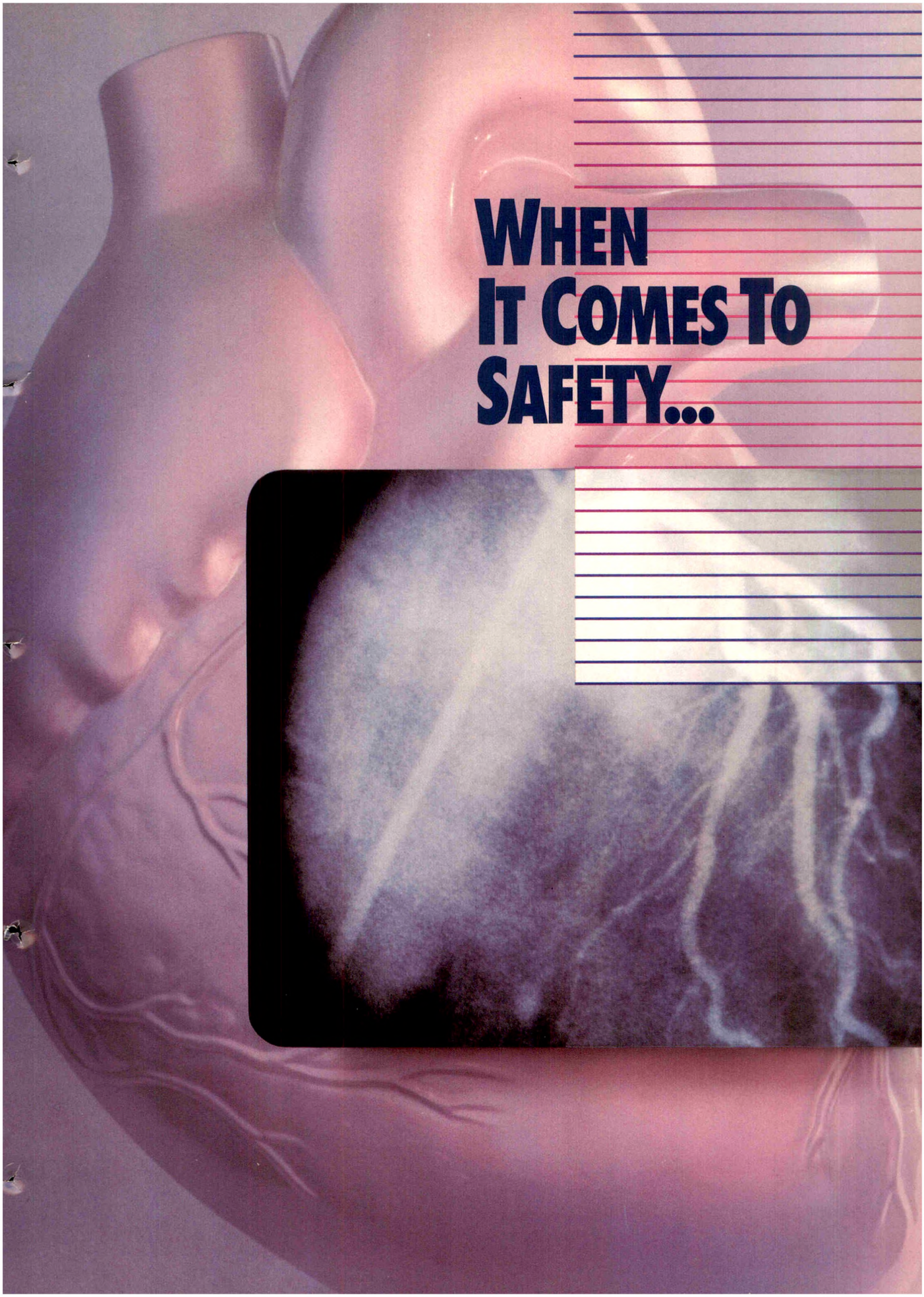
MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

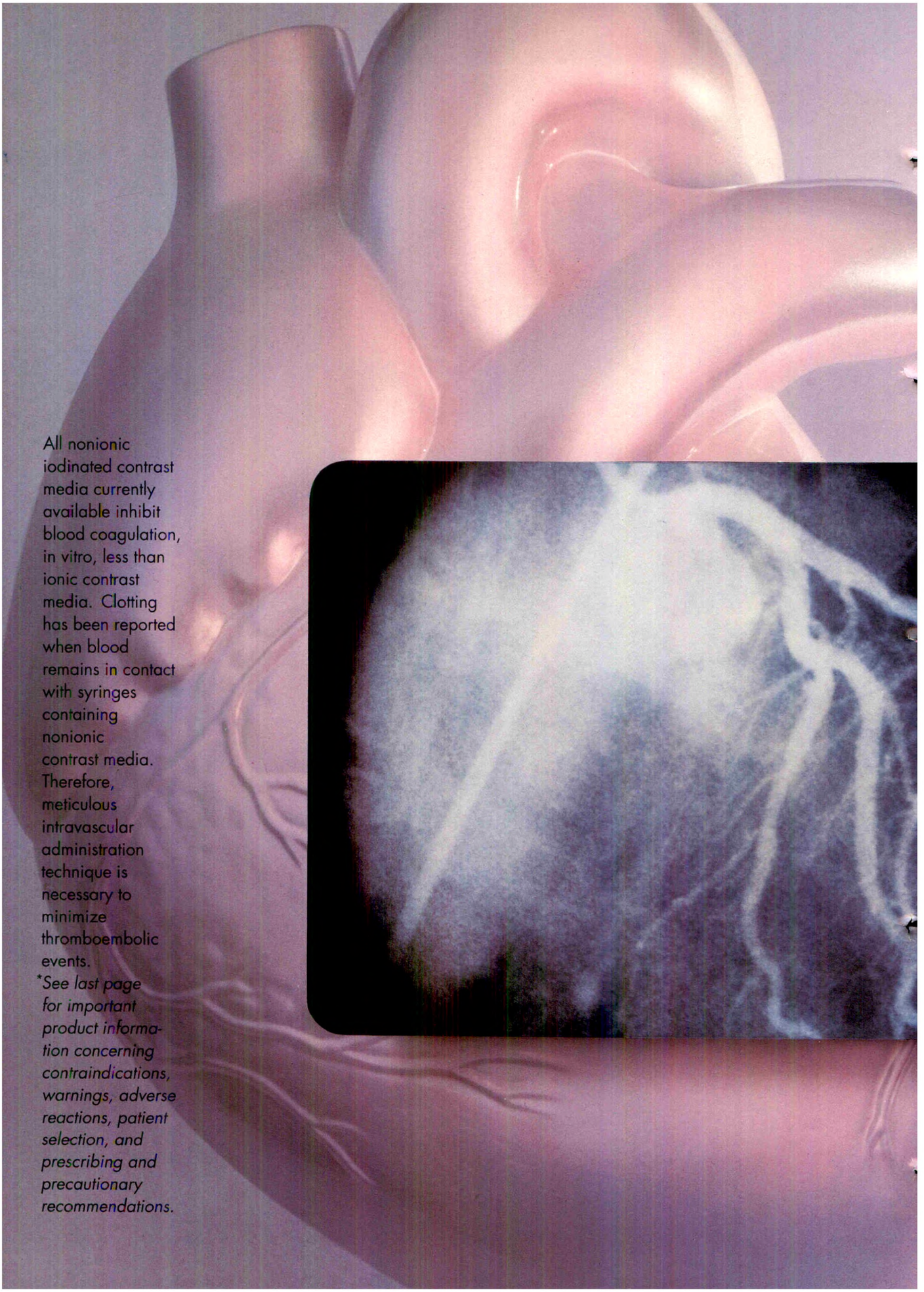
References: 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-1245. 2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651. 3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J. B. et al. (eds.): *The Metabolic Basis of Inherited Disease,* 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642.

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WHEN
IT COMES TO
SAFETY...



All nonionic iodinated contrast media currently available inhibit blood coagulation, in vitro, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary to minimize thromboembolic events.

**See last page for important product information concerning contraindications, warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations.*

WHEN IT COMES TO SAFETY...

ONE IMAGE STANDS OUT.

- No other nonionic or low osmolar contrast medium has demonstrated safety in as many clinical studies as nonionic OMNIPAQUE.
- OMNIPAQUE delivers outstanding image quality.
- OMNIPAQUE is the first second-generation nonionic approved for use in angiocardiography for patients under the age of 18.[1]*
- OMNIPAQUE is used in more cardiac catheterization procedures than any other iodinated contrast agent.[2]

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INTRAVASCULAR

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A SUMMARY FOLLOWS:

DESCRIPTION: OMNIPAQUE is a sterile, pyrogen-free and preservative-free, nonionic, water-soluble radiographic contrast medium for intravascular administration in concentrations of 140, 240, 300, and 350 mgI/mL. OMNIPAQUE 140 contains 302 mg of iohexol equivalent to 140 mg of organic iodine per mL; OMNIPAQUE 240 contains 518 mg of iohexol equivalent to 240 mg of organic iodine per mL; OMNIPAQUE 300 contains 647 mg of iohexol equivalent to 300 mg of organic iodine per mL; and OMNIPAQUE 350 contains 755 mg of iohexol equivalent to 350 mg of organic iodine per mL. Each milliliter of iohexol solution contains 1.21 mg tromethamine and 0.1 mg edetate calcium disodium with the pH adjusted between 6.8 and 7.7 with hydrochloric acid or sodium hydroxide. Unused portions must be discarded. Iohexol solution is sensitive to light and should be protected from exposure.

CONTRAINDICATIONS: OMNIPAQUE should not be administered to patients with a known hypersensitivity to iohexol.

WARNINGS—General: Nonionic iodinated contrast media inhibit blood coagulation, in vitro, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, catheter and syringe material, underlying disease state, and concomitant medications, may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended including close attention to guidewire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing with heparinized saline solutions and minimizing the length of the procedure. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of in vitro clotting.

OMNIPAQUE should be used with extreme care in patients with severe functional disturbances of the liver and kidneys, severe thyrotoxicosis, or myelomatosis. Diabetics with a serum creatinine level above 3 mg/dL should not be examined unless the possible benefits of the examination clearly outweigh the additional risk. OMNIPAQUE is not recommended for use in patients with anuria.

Radiopaque contrast agents are potentially hazardous in patients with multiple myeloma or other paraproteinemia, particularly in those with therapeutically resistant anuria. Although neither the contrast agent nor dehydration has separately proven to be the cause of anuria in myeloma, it has been speculated that the combination of both may be causative factors. The risk in myelomatous patients is not a contraindication; however, special precautions are necessary. Partial dehydration in the preparation of these patients prior to injection is not recommended since this may predispose the patient to precipitation of the myeloma protein in the renal tubules. No form of therapy, including dialysis, has been successful in reversing the effect. Myeloma, which occurs most commonly in persons over age 40, should be considered before instituting intravascular administration of contrast agents.

Ionic contrast media, when injected intravenously or intra-arterially, may promote sickling in individuals who are homozygous for sickle cell disease.

Administration of radiopaque materials to patients known or suspected of having pheochromocytoma should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the procedures may be performed; however, the amount of radiopaque medium injected should be kept to an absolute minimum. The patient's blood pressure should be assessed throughout the procedure and measures for the treatment of hypertensive crisis should be readily available.

Reports of thyroid storm following the use of iodinated, ionic radiopaque contrast media in patients with hyperthyroidism or with an autonomously functioning thyroid nodule suggest that this additional risk be evaluated in such patients before use of any contrast medium.

Urography should be performed with caution in patients with severely impaired renal function and patients with combined renal and hepatic disease.

PRECAUTIONS—General: Diagnostic procedures which involve the use of radiopaque diagnostic agents should be carried out under the direction of personnel with the prerequisite training and with a thorough knowledge of the particular procedure to be performed. Appropriate facilities should be available for coping with any complication of the procedure, as well as for emergency treatment of severe reactions to the contrast agent itself. After parenteral administration of a radiopaque agent, competent personnel and emergency facilities should be available for at least 30 to 60 minutes, since severe delayed reactions have occurred (see ADVERSE REACTIONS: Intravascular—General).

Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, in diabetic patients, and in susceptible nondiabetic patients (often elderly with preexisting renal disease), infants, and small children. Dehydration in these patients seems to be enhanced by the osmotic diuretic action of urographic agents. It is believed that overnight fluid restriction prior to excretory urography generally does not provide better visualization in normal patients. *Patients should be well hydrated prior to and following administration of any contrast medium, including iohexol.*

Acute renal failure has been reported in diabetic patients with diabetic nephropathy and in susceptible nondiabetic patients (often elderly with preexisting renal disease) following excretory urography. Therefore, careful consideration of the potential risks should be given before performing this radiographic procedure in these patients.

Immediately following surgery, excretory urography should be used with caution in renal transplant recipients.

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions should always be considered (see ADVERSE REACTIONS: Intravascular—General). It is of utmost importance that a course of action be carefully planned in advance for immediate treatment of serious reactions, and that adequate and appropriate personnel be readily available in case of any reaction.

The possibility of an idiosyncratic reaction in susceptible patients should always be considered (see ADVERSE REACTIONS: Intravascular—General). The susceptible population includes, but is not limited to, patients with a history of a previous reaction to contrast media, patients with a known sensitivity to iodine per se, and patients with a known clinical hypersensitivity: bronchial asthma, hay fever, and food allergies.

The occurrence of severe idiosyncratic reactions has prompted the use of several pretesting methods. However, pretesting cannot be relied upon to predict severe reactions and may itself be hazardous for the patient. It is suggested that a thorough medical history with emphasis on allergy and hypersensitivity, prior to the injection of any contrast media, may be more accurate than pretesting in predicting potential adverse reactions.

A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent where a diagnostic procedure is thought essential, but caution should be exercised (see ADVERSE REACTIONS: Intravascular—General). Premedication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions in such patients should be considered and administered using separate syringes. Recent reports indicate that such pretreatment does not prevent serious, life-threatening reactions, but may reduce both their incidence and severity.

Even though the osmolality of OMNIPAQUE is low compared to diatrizoate- or iothalamate-based ionic agents of comparable iodine concentration, the potential transitory increase in the circulatory osmotic load in patients with congestive heart failure requires caution during injection. These patients should be observed for several hours following the procedure to detect delayed hemodynamic disturbances.

General anesthesia may be indicated in the performance of some procedures in selected adult patients; however, a higher incidence of adverse reactions has been reported in these patients and may be attributable to the inability of the patient to identify untoward symptoms, or to the hypotensive effect of anesthesia, which can reduce cardiac output and increase the duration of exposure to the contrast agent.

Angiography should be avoided whenever possible in patients with homocystinuria, because of the risk of inducing thrombosis and embolism.

In angiographic procedures, the possibility of dislodging plaques or damaging or perforating the vessel wall should be borne in mind during the catheter manipulations and contrast medium injection. Test injections to ensure proper catheter placement are recommended.

Selective coronary arteriography should be performed only in those patients in whom the expected benefits outweigh the potential risk. The inherent risks of angiocardiography in patients with chronic pulmonary emphysema must be weighed against the necessity for performing this procedure.

When OMNIPAQUE is to be injected using plastic disposable syringes, the contrast medium should be drawn into the syringe and used immediately.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter or discoloration is present, do not use.

Information for Patients: Patients receiving injectable radiopaque diagnostic agents should be instructed to:

1. Inform your physician if you are pregnant.
2. Inform your physician if you are diabetic or if you have multiple myeloma, pheochromocytoma, homozygous sickle cell disease, or known thyroid disorder (see WARNINGS—General).
3. Inform your physician if you are allergic to any drugs, food, or if you had any reactions to previous injections of dyes used for x-ray procedures (see PRECAUTIONS—General).
4. Inform your physician about any other medications you are currently taking, including nonprescription drugs, before you are administered this drug.

Drug/Laboratory Test Interaction: If iodine-containing isotopes are to be administered for the diagnosis of thyroid disease, the iodine-binding capacity of thyroid tissue may be reduced for up to 2 weeks after contrast medium administration. Thyroid function tests which do not depend on iodine estimation, eg, T_3 resin uptake or direct thyroxine assays, are not affected. Many radiopaque contrast agents are incompatible in vitro with some antihistamines and many other drugs; therefore, no other pharmaceuticals should be admixed with contrast agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term animal studies have been performed to evaluate carcinogenic potential, mutagenesis, or whether OMNIPAQUE can affect fertility in men or women.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits with up to 100 times the recommended human dose. No evidence of impaired fertility or harm to the fetus has been demonstrated due to OMNIPAQUE. There are, however, no studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known to what extent iohexol is excreted in human milk. However, many injectable contrast agents are excreted unchanged in human milk. Although it has not been established that serious adverse reactions occur in nursing infants, caution should be exercised when intravascular contrast media are administered to nursing women. Bottle feedings may be substituted for breast feedings for 24 hours following administration of OMNIPAQUE.

Pediatric Use: Pediatric patients at higher risk of experiencing adverse events during contrast medium administration may include those having asthma, a sensitivity to medication and/or allergens, congestive heart failure, a serum creatinine > 1.5 mg/dL, or those less than 12 months of age.

ADVERSE REACTIONS

Intravascular—General: Adverse reactions following the use of OMNIPAQUE are usually mild to moderate in severity. However, serious, life-threatening, and fatal reactions, mostly of cardiovascular origin, have been associated with the administration of iodine-containing contrast media, including OMNIPAQUE. The injection of contrast media is frequently associated with the sensation of warmth and pain, especially in peripheral angiography; pain and warmth are less frequent and less severe with OMNIPAQUE than with many contrast media.

Cardiovascular System: Arrhythmias including PVCs and PACs (2%), angina/chest pain (1%), and hypotension (0.7%). Others including cardiac failure, asystole, bradycardia, tachycardia, and vasovagal reaction were reported with an individual incidence of 0.3% or less. In controlled clinical trials involving 1,485 patients, one fatality occurred. A cause and effect relationship between this death and iohexol has not been established.

Nervous System: Vertigo [including dizziness and lightheadedness] (0.5%), pain (3%), vision abnormalities [including blurred vision and photomas] (2%), headache (2%), and taste perversion (1%). Others including anxiety, blurred vision, fever, motor and speech dysfunction, convulsion, paresthesia, somnolence, stiff neck, hemiparesis, syncope, shivering, transient ischemic attack, cerebral infarction, and nystagmus were reported, with an individual incidence of 0.3% or less.

Respiratory System: Dyspnea, rhinitis, coughing, and laryngitis, with an individual incidence of 0.2% or less.

Gastrointestinal System: Nausea (2%) and vomiting (0.7%). Others including diarrhea, dyspepsia, cramp, and dry mouth were reported, with an individual incidence of less than 0.1%.

Skin and Appendages: Urticaria (0.3%), purpura (0.1%), abscess (0.1%), and pruritus (0.1%).

Individual adverse reactions which occurred to a significantly greater extent for a specific procedure are listed under that indication in full prescribing information.

Pediatrics: In controlled clinical trials involving 391 patients for pediatric angiocardiography, urography, and contrast-enhanced computed tomographic head imaging, adverse reactions following the use of OMNIPAQUE 240, OMNIPAQUE 300 and OMNIPAQUE 350 were generally less frequent than with adults.

Cardiovascular System: Ventricular tachycardia (0.5%), 2:1 heart block (0.5%), hypertension (0.3%), and anemia (0.3%).

Nervous System: Pain (0.8%), fever (0.5%), taste abnormality (0.5%), and convulsion (0.3%).

Respiratory System: Congestion (0.3%) and apnea (0.3%).

Gastrointestinal System: Nausea (1%), hypoglycemia (0.3%), and vomiting (2%).

Skin and Appendages: Rash (0.3%).

General Adverse Reactions to Contrast Media: Physicians should remain alert for the occurrence of adverse effects in addition to those discussed above. The following reactions have been reported after administration of other intravascular iodinated contrast media, and rarely with iohexol. *Reactions due to technique:* hematomas and ecchymoses. *Hemodynamic reactions:* vein cramp and thrombophlebitis following intravenous injection. *Cardiovascular reactions:* rare cases of cardiac arrhythmias, reflex tachycardia, chest pain, cyanosis, hypertension, hypotension, peripheral vasodilatation, shock, and cardiac arrest. *Renal reactions:* occasionally, transient proteinuria, and rarely, oliguria or anuria. *Allergic reactions:* asthmatic attacks, nasal and conjunctival symptoms, dermal reactions such as urticaria with or without pruritus, as well as pleomorphic rashes, sneezing, and lacrimation, and rarely, anaphylactic reactions. Rare fatalities have occurred due to this or unknown causes. *Signs and symptoms related to the respiratory system:* pulmonary or laryngeal edema, bronchospasm, dyspnea; *or to the nervous system:* restlessness, tremors, convulsions. *Other reactions:* flushing, pain, warmth, metallic taste, nausea, vomiting, anxiety, headache, confusion, pallor, weakness, sweating, localized areas of edema (especially facial cramps), neutropenia, and dizziness. Rarely, immediate or delayed rigors can occur, sometimes accompanied by hyperpyrexia. Infrequently, "iodism" (salivary gland swelling) from organic iodinated compounds appears 2 days after exposure and subsides by the sixth day.

In general, the reactions which are known to occur upon parenteral administration of iodinated contrast agents are possible with any nonionic agent. Approximately 95% of adverse reactions accompanying the use of water-soluble intravascularly administered contrast agents are mild to moderate in degree. However, severe, life-threatening anaphylactoid reactions, mostly of cardiovascular origin, have occurred. Reported incidences of death range from 6.6 per 1 million (0.00066%) to 1 in 10,000 (0.01%). Most deaths occur during injection or 5 to 10 minutes later, the main feature being cardiac arrest, with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. The incidence of shock is estimated to be 1 out of 20,000 (0.005%) patients.

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions.

Chemotoxic reactions result from the physicochemical properties of the contrast media, the dose, and the speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the amount of dose injected, the speed of injection, and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate, and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

The reported incidence of adverse reactions to contrast media in patients with a history of allergy is twice that in the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations.

Most adverse reactions to injectable contrast media appear within 1 to 3 minutes after the *start of injection, but* delayed reactions may occur.

Regardless of the contrast agent employed, the overall estimated incidence of serious adverse reactions is higher with angiocardiography than with other procedures. Cardiac decompensation, serious arrhythmias, angina pectoris, or myocardial ischemia or infarction may occur during angiocardiography and left ventriculography. Electrocardiographic and hemodynamic abnormalities occur less frequently with OMNIPAQUE than with diatrizoate meglumine and diatrizoate sodium injection.

CONSULT PACKAGE INSERT FOR A MORE DETAILED DISCUSSION OF ADVERSE REACTIONS FOR INTRAVASCULAR USE OF OMNIPAQUE.

OVERDOSAGE: Overdosage may occur. The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular systems. The symptoms include cyanosis, bradycardia, acidosis, pulmonary hemorrhage, convulsions, coma, and cardiac arrest. Treatment of an overdosage is directed toward the support of all vital functions and prompt institution of symptomatic therapy.

The intravenous LD_{50} values of OMNIPAQUE (in grams of iodine per kilogram body weight) are 24.2 in mice and 15.0 in rats.

DOSAGE AND ADMINISTRATION: Details are provided in the package insert.

References:
1. Data on file, Winthrop Pharmaceuticals.
2. Market Measures, 1989.

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1049

Circadian Rhythm of Heart Rate Variability After Acute Myocardial Infarction and Its Influence on the Prognostic Value of Heart Rate Variability

Marek Malik, Thomas Farrell, and A. John Camm

Heart rate (HR) variability was measured in 20 patients who initially survived acute myocardial infarction (AMI) but later experienced serious events (group I) and in 20 patients who remained free of complications for >6 months after discharge (group II). Both groups were matched with regard to age, gender, infarct size, ejection fraction, and β-blocker treatment. HR variability was assessed in the 24-hour electrocardiograms recorded during the first 2 weeks after AMI and in various portions of the complete recording. The maximum reduction of HR variability in the group I patients was found in recordings starting approximately at 6 A.M. and lasting for approximately 8 hours. In patients at low risk of sudden cardiac death or serious arrhythmic events, or both, after an AMI, the diurnal rhythm of HR variability is more marked than it is in high-risk patients, and long-term components of HR variability must be included in the measurement of HR variability when using it as a long-term predictor of risk after an AMI, because of diurnal variation.

1055

Doppler Assessment of Left Ventricular Filling Pattern in Silent Ischemia in Patients with Prinzmetal's Angina

Elisabetta Doria, Piergiuseppe Agostoni, Alessandro Loaldi, and Cesare Fiorentini

In 6 patients, left ventricular (LV) diastolic function was studied during 16 episodes of spontaneous angina by simultaneous recordings of electrocardiographic (ECG), echocardiographic, pulsed Doppler and hemodynamic parameters. We demonstrated the existence of 3 distinct phases during the ischemic attacks: (1) "waxing" phase: transmitral flow changes with minimal ECG modifications; (2) "steady" phase: maximal ECG changes; and (3) "waning" phase: regression of the ECG changes. In each phase transmitral Doppler flow tracings showed significant changes only in early diastole. This implies that myocardial ischemia affects mainly the early phase of diastole. Furthermore, LV diastolic dysfunction preceded systolic abnormalities. In the waning phase all the recorded parameters were consistent with LV "contractile rebound" affecting both diastole and systole.

1060

Aortic Calcified Plaques and Cardiovascular Disease (The Framingham Study)

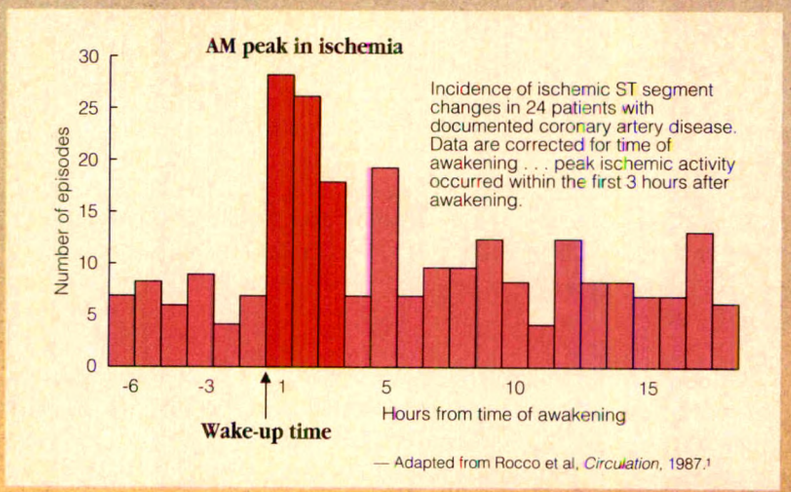
Jacqueline C. M. Witteman, William B. Kannel, Philip A. Wolf, Diederick E. Grobbee, Albert Hofman, Ralph B. D'Agostino, and Janet C. Cobb

The relation between the presence of calcified plaques in the thoracic aorta, as detected on chest x-rays, and subsequent cardiovascular disease is examined during 12 years of follow-up of the Framingham cohort (n = 5,209). The presence of aortic calcified plaques was associated with a

Continued on page A27

As predictable as the sunrise…

The morning rise in myocardial ischemia[1]



Studies indicate that a similar circadian pattern also exists for:

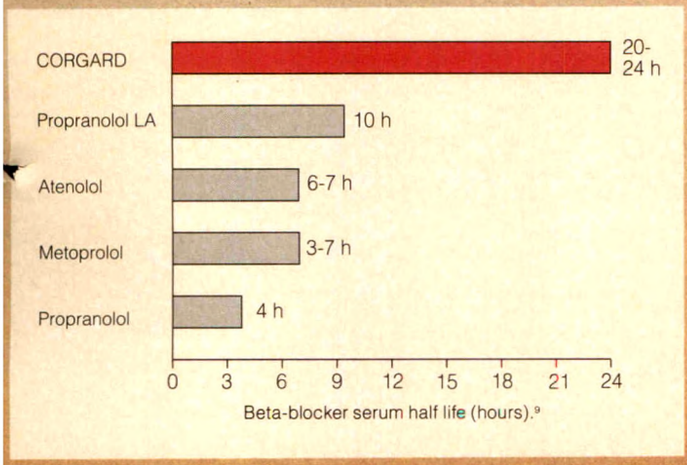
- —Myocardial infarction[2]
- —Sudden cardiac death[3]
- —Ischemic stroke[4]
- —Heart rate[5]
- —Blood pressure[5]
- —Plasma catecholamines[6]
- —Platelet aggregation.[6]

Corgard® (nadolol tablets) is not indicated for treatment or prevention of myocardial infarction, sudden cardiac death, or ischemic stroke.

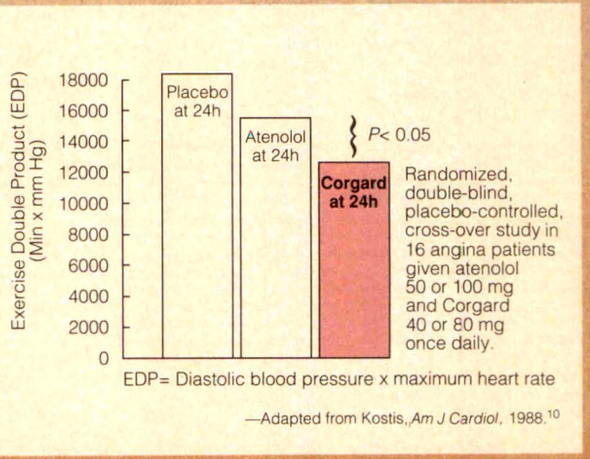
CORGARD

24-hour antianginal protection… throughout the circadian pattern of myocardial ischemia[7]

Corgard: The beta blocker with the longest duration of action[8]… and the longest half life[9]



Corgard: Significantly greater suppression of exercise double product than atenolol at 24 hours[10]



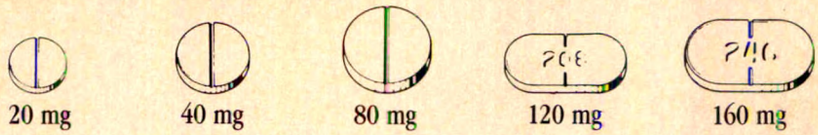
CORGARD®

(nadolol tablets)

On guard, 24 hours a day

Please see brief summary of prescribing information on adjacent page.

CORGARD®
(nadolol tablets)
On guard, 24 hours a day



CORGARD® TABLETS
Nadolol Tablets USP

DESCRIPTION: CORGARD (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery—Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function—Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients—Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug Interactions—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect; monitor closely for hypotension and/or excessive bradycardia.

Carcinogenesis, Mutagenesis, Impairment of Fertility—In 1 to 2 year oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy Category C—In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

Nursing Mothers—Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular—Bradycardia with heart rates of less than 50 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**—Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**— Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia.

The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System**—reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**—fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**— pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm—Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE—For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg qd; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg qd (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg qd; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg qd (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information consult package insert.

HOW SUPPLIED: In scored tablets containing 20, 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100. The 40 mg, 80 mg, and 120 mg tablets are available in bottles of 1000 tablets. The 20 mg, 40 mg, and 80 mg tablets are also available in Unimatic® unit-dose packs of 100 tablets.

(J4-156)

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References: 1. Rocco MB, Barry J, Campbell S, et al: Circadian variation of transient myocardial ischemia in patients with coronary artery disease. *Circulation* 75:395-400;1987. 2. Muller JE, Stone PH, Turi ZG, et al: Circadian variation in the frequency of onset of acute myocardial infarction. *N Engl J Med* 313:1315-1322;1985. 3. Willich SN, Levy D, Rocco MB, Tofler GH, Stone PH, Muller JE: Circadian variation in the incidence of sudden cardiac death in the Framingham Heart Study population. *Am J Cardiol* 60:801-806;1987. 4. Marler JR, Price TR, Clark GL, et al: Morning increase in onset of ischemic stroke. *Stroke* 20:473-476;1989. 5. Millar-Craig MW, Bishop CN, Raftery EB: Circadian variation of blood-pressure. *Lancet* 1:795-797;1978. 6. Tofler GH, Brezinski D, Schafer AI, et al: Concurrent morning increase in platelet aggregability and the risk of myocardial infarction and sudden cardiac death. *N Engl J Med* 316:1514-1518;1987. 7. Kostis JB, Lacy CR, Krieger SD, et al: Atenolol, nadolol, and pindolol in angina pectoris on effort: effect of pharmacokinetics. *Am Heart J* 108:1131-1136;1984. 8. Vukovich RA, Foley JE, Brown B, et al: Effect of β-blockers on exercise double product (systolic blood pressure × heart rate). *Br J Clin Pharmacol* 7(suppl 2): 167S-172S;1979. 9. *Physicians' Desk Reference®*, ed 43, Medical Economics Company, Inc., Oradell, NJ, 1989, pp. 969, 1037, 1635, 2306, 2308. 10. Kostis JB: Comparison of the duration of action of atenolol and nadolol for treatment of angina pectoris. *Am J Cardiol* 62:1171-1175;1988.

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R-K43

Issued: February 1990

twofold increase in risk of cardiovascular death in men and women aged <65 years, even after other risk factors were taken into account. Similar increases in risk were found for coronary artery disease, stroke and intermittent claudication among middle-aged women, but among middle-aged men these risks were less marked. No excess risk was observed for subjects aged ≥65 years. Thus, the finding of aortic calcified plaques on a chest x-ray in a relatively young subject indicates an increased risk of cardiovascular disease.

1065

Comparison of Direct and Indirect Measures of Systemic Arterial Pressure During Weightlifting in Coronary Artery Disease

Elizabeth M. Wiecek, Neil McCartney, and Robert S. McKelvie

Direct and indirect measures of arterial pressure during weightlifting in 5 men with coronary artery disease were compared. Subjects did 15 repetitions of single-arm curl, single-arm military press, and single- and double-leg press at submaximal loads. The indirect measures of systolic pressure were 8 to 16% less than ($p < 0.01$) those recorded directly, but diastolic pressures were similar. The highest intraarterial pressures occurred during the final repetitions of the set, followed by a rapid decrease in both systolic and diastolic pressure. It is concluded that indirect estimates of systolic pressure are significantly less than true arterial values at rest, and during and after lifting. Furthermore, indirect measurements after lifting are a poor reflection of the arterial pressures generated during lifting because of the rapid decrease in pressure that occurs after exercise. For example, mean systolic pressure recorded indirectly immediately after the arm exercises was 76 torr (34%) less than the average peak intraarterial value.

1070

Response of Angiographically Normal and Atherosclerotic Left Anterior Descending Coronary Arteries to Acetylcholine

Christopher M. Newman, Attilio Maseri, David R. Hackett, Hassan M. El-Tamimi, and Graham J. Davies

We examined the effects of increasing concentrations of intracoronary acetylcholine on successive segments of the coronary circulation in 10 patients with angiographically normal coronary arteries (group 1) and in 7 patients with coronary atherosclerosis (group 2). In group 1, acetylcholine caused minor (≤6%) but progressive dilatation of the left anterior descending artery (LAD) up to 10^{-4}M, changing to predominantly distal epicardial vessel constriction at higher concentrations. Systemic and left ventricular hemodynamics remained unchanged, but coronary sinus oxygen saturation rose progressively from a basal level of 36 ± 3 to a maximum of 72 ± 3%, indicating marked progressive dilatation of resistance vessels. In group 2, acetylcholine (infused only up to 10^{-4}M for ethical reasons) failed to cause significant changes in LAD diameter. Both acetylcholine concentration and the coronary vascular segment under study are important determinants of the observed response, suggesting that a constrictor response to intracoronary acetylcholine is not always "paradoxical" and an indicator of coronary atherosclerosis.

Continued on page A30

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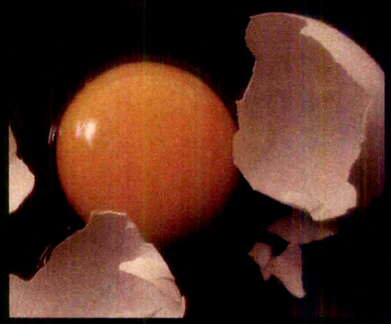
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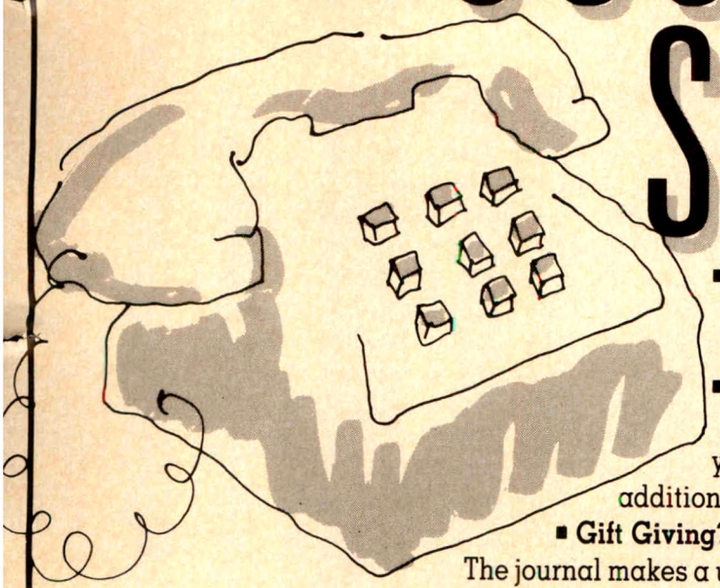
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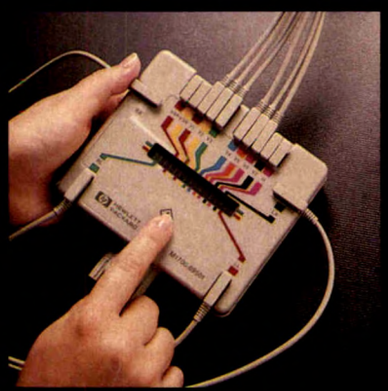
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1077
Intraoperative Myocardial Contrast Echocardiography for Assessment of Regional Bypass Perfusion
Harald Mudra, Werner Zwehl, Volker Klauss, Eckart Kreuzer, Mathias C. Haufe, Christiane Angermann, and Karl Theisen

To assess regional bypass-dependent myocardial blood flow, sonicated iopromid (2 ml, microbubble size 6 ± 4 μm) was injected into 11 grafts in 8 men (mean age 61 years) during routine coronary bypass surgery after completion of electromagnetic flow measurements. Epicardial echocardiography was performed simultaneously. In 10 of 11 grafts, a clear myocardial opacification resulted. Computer-assisted evaluation by videodensitometry resulted in time-intensity curves with contrast decay half-times (T½) from 2.2 to 6.9 seconds (mean 4.3 ± 1.4), which did not correlate with flow measured using electromagnetic flow probes. No adverse effects occurred. Thus, myocardial contrast echocardiography is a safe and feasible method for evaluating coronary bypass grafts intraoperatively, and may have impact on surgical strategies.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

1082
Clinical and Electrophysiologic Characteristics of Patients with Antidromic Circus Movement Tachycardia in the Wolff-Parkinson-White Syndrome
Jacob Atié, Pedro Brugada, Josep Brugada, Joep L.R.M. Smeets, Fernando E.S. Cruz, Ayrton Peres, Marie P. Roukens, and Hein J.J. Wellens

Antidromic circus movement tachycardia was documented in 36 of 345 consecutive patients with the Wolff-Parkinson-White syndrome. Multiple accessory pathways were identified in 12 of these 36 patients. Four patients were resuscitated from ventricular fibrillation. In the 36 patients, 56 distinct antidromic tachycardias were recorded and several different pathways were observed.

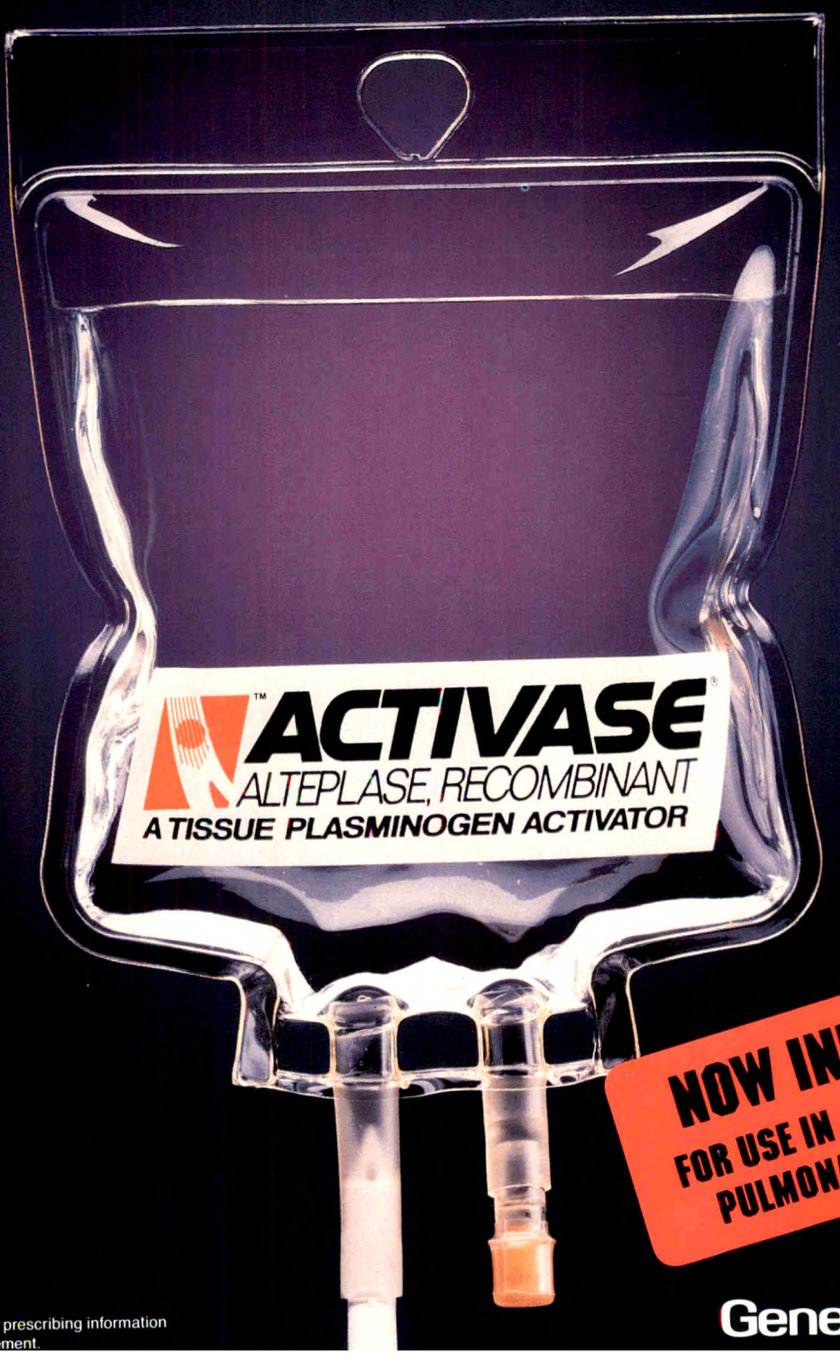
1092
Persistence of Arrhythmia Exercise Response in Healthy Young Men
Yaacov Drory, Amos Pines, Enrique Z. Fisman, and Jan J. Kellermann

Arrhythmia was again present in 60% of 76 young men after a mean interval of 6.7 years had elapsed from the time of their initial examination, when their arrhythmias were observed at rest or during exercise tests, or both. None of the patients had structural heart disease. At follow-up, the rate of persistence did not differ significantly between ventricular and supraventricular arrhythmic patients, or among those who had had different response patterns to exercise tests on their initial examination. Patterns of arrhythmia did not change from the initial findings in almost all of the patients in whom arrhythmia was again demonstrated at follow-up. The large percentage of our patients whose arrhythmias were still present after

Continued on page A34

IN ACUTE MI

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NOW INDICATED
FOR USE IN ACUTE MASSIVE PULMONARY EMBOLISM

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Genentech, Inc.



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- No reported episodes of infusion-related hypotension requiring emergency intervention

Bleeding is the most common complication of thrombolytic therapy, with intracranial bleeding being the most serious. Activase® is contraindicated in patients with: active internal bleeding, history of cerebrovascular accident, recent (within two months) intracranial or intraspinal surgery or trauma, intracranial neoplasm, arteriovenous malformation, or aneurysm, known bleeding diathesis, severe uncontrolled hypertension. (See WARNINGS section of brief summary of prescribing information.)

NOW INDICATED
FOR USE IN ACUTE MASSIVE PULMONARY EMBOLISM

Genentech, Inc.

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When a life is on the line

ACTIVASE®
ALTEPLASE, RECOMBINANT
A TISSUE PLASMINOGEN ACTIVATOR

Please see brief summary of prescribing information on facing page

ACTIVASE®
ALTEPLASE, RECOMBINANT
A TISSUE PLASMINOGEN ACTIVATOR

Brief Summary
Consult full prescribing information before using.

INDICATIONS AND USAGE: ACTIVASE® is indicated for use in the management of acute myocardial infarction (AMI) in adults for the lysis of thrombi obstructing coronary arteries, the reduction of infarct size, the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms.

ACTIVASE® is also indicated in the management of acute massive pulmonary embolism (PE) in adults: for the lysis of acute pulmonary emboli, defined as obstruction of blood flow to a lobe or multiple segments of the lungs, and for the lysis of pulmonary emboli accompanied by unstable hemodynamics, i.e., failure to maintain blood pressure without supportive measures. The diagnosis should be confirmed by objective means, such as pulmonary angiography or noninvasive procedures such as lung scanning.

CONTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding, ACTIVASE® is contraindicated in the following situations: • Active internal bleeding • History of cerebrovascular accident • Recent (within two months) intracranial or intraspinal surgery or trauma (see WARNINGS) • Intracranial neoplasm, arteriovenous malformation, or aneurysm • Known bleeding diathesis • Severe uncontrolled hypertension.

WARNINGS: Bleeding The most common complication encountered during ACTIVASE® therapy is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

Concomitant use of heparin anticoagulation may contribute to bleeding. Some hemorrhagic episodes occurred one or more days after the effects of ACTIVASE® had dissipated, but while heparin therapy was continuing.

As fibrin is lysed during ACTIVASE® therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including sites of catheter insertion, arterial and venous puncture, cutdown and needle puncture).

Intramuscular injections and nonessential handling of the patient should be avoided during treatment with ACTIVASE®. Venipunctures should be performed carefully and only as required.

Should an arterial puncture be necessary during an infusion of ACTIVASE®, it is preferable to use an upper extremity vessel accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding.

Should serious bleeding (not controllable by local pressure) occur, the infusion of ACTIVASE® and any concomitant heparin should be terminated immediately.

Each patient being considered for therapy with ACTIVASE® should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

In the following conditions, the risks of ACTIVASE® therapy may be increased and should be weighed against the anticipated benefits: • Recent (within 10 days) major surgery, e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels • Cerebrovascular disease • Recent (within 10 days) gastrointestinal or genitourinary bleeding • Recent (within 10 days) trauma • Hypertension: systolic BP≥180 mm Hg and/or diastolic BP≥110 mm Hg • High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation • Acute pericarditis • Subacute bacterial endocarditis • Hemostatic defects including those secondary to severe hepatic or renal disease • Significant liver dysfunction • Pregnancy • Diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions • Septic thrombophlebitis or occluded AV cannula at seriously infected site • Advanced age, i.e., over 75 years old • Patients currently receiving oral anticoagulants • Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Arrhythmias Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias are not different from those often seen in the ordinary course of AMI and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when infusions of ACTIVASE® are administered.

Pulmonary Embolism It should be recognized that the treatment of pulmonary embolism with ACTIVASE®, Alteplase, has not been shown to constitute adequate clinical treatment of underlying deep vein thrombosis. Furthermore, the possible risk of reembolization due to the lysis of underlying deep venous thrombi should be considered.

PRECAUTIONS: General Standard management of myocardial infarction or pulmonary embolism should be implemented concomitantly with ACTIVASE® treatment. Noncompressible arterial puncture must be avoided. Arterial and venous punctures should be minimized. In the event of serious bleeding, ACTIVASE® and heparin should be discontinued immediately. Heparin effects can be reversed by protamine.

Readministration There is no experience with readministration of ACTIVASE®. If anaphylactoid reaction occurs, infusion should be discontinued immediately and appropriate therapy initiated.

Although sustained antibody formation in patients receiving one dose of ACTIVASE® has not been documented, readministration should be undertaken with caution.

Laboratory Tests During ACTIVASE® therapy, results of coagulation tests and/or measures of fibrinolytic activity may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. ACTIVASE® is an enzyme that when present in blood in pharmacologic concentrations remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (150-200 units/mL) can to some extent mitigate this phenomenon.

Drug Interactions The interaction of ACTIVASE® with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function (such as acetylsalicylic acid, dipyridamole) may increase the risk of bleeding if administered prior to, during or after ACTIVASE® therapy.

Use of Anticoagulants Heparin has been administered concomitantly with and following infusions of ACTIVASE® to reduce the risk of rethrombosis. Because either heparin or ACTIVASE® alone may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites.

Pregnancy (Category C) Animal reproduction studies have not been conducted with ACTIVASE®. It is also not known whether ACTIVASE® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ACTIVASE® should be given to a pregnant woman only if clearly needed.

Pediatric Use Safety and effectiveness of ACTIVASE® in children has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Short-term studies, which evaluated tumorigenicity of ACTIVASE® and effect on tumor metastases in rodents, were negative.

Studies to determine mutagenicity (Ames test) and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested. Cytotoxicity, as reflected by a decrease in mitotic index, was evidenced only after prolonged exposure and only at the highest concentrations tested.

Nursing Mothers It is not known whether ACTIVASE® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ACTIVASE® is administered to a nursing woman.

ADVERSE REACTIONS: Bleeding The most frequent adverse reaction associated with ACTIVASE® is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

The following incidence of significant internal bleeding (estimated as >250 cc blood loss) has been reported in studies in over 800 patients treated at all doses:

	Total Dose ≤ 100 mg	Total Dose > 100 mg
gastrointestinal	5%	5%
genitourinary	4%	4%
ecchymosis	1%	<1%
retroperitoneal	<1%	<1%
epistaxis	<1%	<1%
gingival	<1%	<1%

The incidence of intracranial bleeding in patients treated with ACTIVASE®, Alteplase, recombinant, is as follows:

Dose	Number of Patients	%
100 mg	3272	0.4
150 mg	1779	1.3
1-1.4 mg/kg	237	0.4

These data indicate that a dose of 150 mg of ACTIVASE® should not be used because it has been associated with an increase in intracranial bleeding.

Recent data indicate that the incidence of stroke in 6 randomized double-blind placebo controlled trials[1-7] is not signficantly different in the ACTIVASE® treated patients compared to those treated with placebo (37/3161, 1.2% versus 27/3092, 0.9%, respectively) ($p = 0.26$).

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, ACTIVASE® therapy should be discontinued immediately, along with any concomitant therapy with heparin.

Fibrin, which is part of the hemostatic plug formed at needle puncture sites, will be lysed during ACTIVASE® therapy. Therefore, ACTIVASE® therapy requires careful attention to potential bleeding sites.

Allergic Reactions No serious or life-threatening allergic reactions have been reported. Other mild hypersensitivity reactions such as urticaria have been observed occasionally.

Other Adverse Reactions Other adverse reactions have been reported, principally nausea and/or vomiting, hypotension, and fever. These reactions are frequent sequelae of MI and may or may not be attributable to ACTIVASE® therapy.

DOSAGE AND ADMINISTRATION: ACTIVASE® is for intravenous administration only. **ACUTE MYOCARDIAL INFARCTION: Administer ACTIVASE® as soon as possible after the onset of symptoms.**

The recommended dose is 100 mg administered as 60 mg (34.8 million IU) in the first hour (of which 6 to 10 mg is administered as a bolus over the first 1-2 minutes), 20 mg (11.6 million IU) over the second hour, and 20 mg (11.6 million IU) over the third hour. For smaller patients (less than 65 kg), a dose of 1.25 mg/kg administered over 3 hours, as described above, may be used.[8]

Although the use of anticoagulants and antiplatelet drugs during and following administration of ACTIVASE® has not been shown to be of unequivocal benefit, heparin has been administered concomitantly for 24 hours or longer in more than 90% of patients. Aspirin and/or dipyridamole have been given either during and/or following heparin treatment.

PULMONARY EMBOLISM: The recommended dose is 100 mg administered by intravenous infusion over two hours. Heparin therapy should be instituted or reinstituted near the end of or immediately following the ACTIVASE® infusion when the partial thromboplastin time or thrombin time returns to twice normal or less.

A DOSE OF 150 MG OF ACTIVASE® SHOULD NOT BE USED BECAUSE IT HAS BEEN ASSOCIATED WITH AN INCREASE IN INTRACRANIAL BLEEDING.

Reconstitution and Dilution DO NOT USE IF VACUUM IS NOT PRESENT.

ACTIVASE® should be reconstituted by aseptically adding the appropriate volume of the accompanying Sterile Water for Injection, USP to the vial. It is important that ACTIVASE® be reconstituted only with Sterile Water for Injection, USP, without preservatives. Do not use Bacteriostatic Water for Injection, USP. The reconstituted preparation results in a colorless to pale yellow transparent solution containing ACTIVASE® 1.0 mg/mL at approximately pH 7.3. The osmolality of this solution is approximately 215 mOsm/kg.

Because ACTIVASE® contains no antibacterial preservatives, it should be reconstituted immediately before use. The solution may be used for intravenous administration within 8 hours following reconstitution when stored between 2-30°C. Before further dilution or administration, the product should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

ACTIVASE® may be administered as reconstituted at 1.0 mg/mL. As an alternative, the reconstituted solution may be diluted further immediately before administration in an equal volume of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to yield a concentration of 0.5 mg/mL. Either polyvinyl chloride bags or glass bottles are acceptable. ACTIVASE® is stable for up to 8 hours in these solutions at room temperature. Exposure to light has no effect on the stability of these solutions. Excessive agitation during dilution should be avoided; mixing should be accomplished with gentle swirling and/or slow inversion. Do not use other infusion solutions, e.g., Sterile Water for Injection, USP or preservative-containing solutions for further dilution.

No other medication should be added to infusion solutions containing ACTIVASE®. Any unused infusion solution should be discarded.

HOW SUPPLIED: ACTIVASE® is supplied as a sterile, lyophilized powder in 20 mg and 50 mg vials containing vacuum, each packaged with diluent for reconstitution.

Storage Store lyophilized ACTIVASE® at controlled room temperature not to exceed 30°C (86°F), or under refrigeration (2-8°C/36-46°F). Protect the lyophilized material during extended storage from excessive exposure to light.

Do not use beyond the expiration date stamped on the vial.

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ACTIVASE®, Alteplase, recombinant
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a time lapse of 3 to 16 years justifies further inquiry into this issue. However, arrhythmia without underlying heart disease would seem to reflect a benign natural history in these young men at this time.

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Electrocardiographic Signal-Averaging During Atrial Pacing and Effect of Cycle Length on the Terminal QRS in Patients With and Without Inducible Ventricular Tachycardia

Mark S. Kremers, William H. Black, Richard Lange, Peter J. Wells, and Martha Solo

Signal-averaged electrocardiograms were recorded during sinus rhythm and atrial pacing in 15 patients without (group 1) and 7 patients with (group 2) inducible sustained ventricular tachycardia (VT). In sinus rhythm (79 ± 12 vs 77 ± 12 beats/min, difference not significant), the duration of the low-amplitude signal (LAS) <40 μV was longer in group 2 than in group 1 (43 ± 21 vs 26 ± 8 ms, $p = 0.034$) but QRS duration (121 ± 32 vs 98 ± 19) and terminal QRS voltage (33 ± 33 vs 50 ± 26) were not significantly different. With atrial pacing in group 1 (128 ± 16 beats/min), mean QRS duration (98 ± 19 vs 97 ± 12) and LAS terminal QRS duration (26 ± 8 vs 25 ± 11) were unchanged and terminal root mean square voltage increased (50 ± 26 to 59 ± 40). With atrial pacing in group 2 (119 ± 12 beats/min), mean QRS duration (121 ± 32 vs 122 ± 28) and terminal QRS duration (93 ± 21 vs 42 ± 16) were also unchanged but terminal voltage decreased (33 ± 33 to 22 ± 23) and became significantly different from group 1 ($p = 0.017$). The signal-averaged electrocardiogram is largely independent of heart rate, but terminal root mean square voltage decreases in patients with inducible VT. This may be the result of decremental conduction in arrhythmogenic tissue.

1099

Reproducibility in Circadian Rhythm of Ventricular Premature Complexes

Gaetano A. Lanza, Maria C. Cortellessa, Antonio G. Rebuzzi, Enrico V. Scabbia, Alessandra Costalunga, Sergio Tamburi, Michele Lucente, and Ugo Manzoli

The existence and reproducibility of a circadian rhythm of ventricular premature complexes (VPCs) were evaluated in 38 patients (19 with coronary artery disease and 19 with structurally normal hearts) during 2 days of Holter monitoring. Chronobiologic analysis was made by cosinor methods. A significant circadian rhythm of VPCs was found both on the first day (mesor 399, acrophase at 15:08 [3:08 P.M.]; $p < 0.01$) and on the second day (mesor 306, acrophase at 14:47 [2:47 P.M.], $p < 0.05$) in the total sample. The circadian trend of VPCs was strongly similar on the 2 days and showed 2 peaks, the first in the morning and the second in the afternoon. Individual rhythms of VPCs were significant on both days in 18 patients (47%, group A), whereas 20 (group B) did not show a significant rhythm in ≥1 day. A high reproducibility of the individual rhythm of VPCs was found in group A patients (difference between the acrophases of the 2 days = 2.1 ± 1.8 hours). Group A patients were older, whereas the reproducibility of the circadian rhythm of VPCs was not influenced by gender, coronary artery disease, therapy, basal VPC number and mean day-to-day variability of VPCs.

Continued on page A40

TENORMIN makes a lifesaving difference.

The TENORMIN regimen (I.V. Injection followed by Tablets) increases survival in acute and post-MI.

The lifesaving benefits of TENORMIN were firmly established in a study of 16,027 patients with suspected acute myocardial infarction.[1] Appropriate patients received an immediate IV injection followed by oral therapy. Week-one mortality was reduced by 15%. However, when therapy was initiated within 2 hours of the onset of pain, week-one mortality was decreased by 53% compared to conventional therapy alone.† Therapy with TENORMIN Tablets may be continued for 3 years.[2]*

**Good clinical judgment suggests that patients who are dependent on sympathetic stimulation for adequate cardiac output and BP are not good candidates for beta blockade. In addition to patients excluded from the ISIS-1 study, those with borderline BP (ie, systolic <120, especially if over age 60) are less likely to benefit.*

† Data derived.



A right start for the long run.

I.V. INJECTION/TABLETS

TENORMIN®

(atenolol)

See adjacent page for references and brief summary of prescribing information.

A right start for the long run.

I.V. INJECTION/TABLETS

TENORMIN®

(atenolol)

BRIEF SUMMARY (For full prescribing information, see package insert.)

INDICATIONS AND USAGE: Hypertension: TENORMIN is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

Angina Pectoris Due to Coronary Atherosclerosis: TENORMIN is indicated for the long-term management of patients with angina pectoris.

Acute Myocardial Infarction: TENORMIN is indicated in the management of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment can be initiated as soon as the patient's clinical condition allows. (See DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS.) In general, there is no basis for treating patients like those who were excluded from the ISIS-1 trial (blood pressure less than 100 mm Hg systolic, heart rate less than 50 bpm) or have other reasons to avoid beta blockade. As noted above, some subgroups (eg, elderly patients with systolic blood pressure below 120 mm Hg) seemed less likely to benefit.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure. (See WARNINGS.)

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In patients who have congestive heart failure controlled by digitalis and/or diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In patients with acute myocardial infarction, cardiac failure which is not promptly and effectively controlled by 80 mg of intravenous furosemide or equivalent therapy is a contraindication to beta-blocker treatment.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues despite adequate digitalization and diuresis, TENORMIN should be withdrawn. (See DOSAGE AND ADMINISTRATION.)

Cessation of Therapy with TENORMIN: Patients with coronary artery disease, who are being treated with TENORMIN, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with beta blockers. The last two complications may occur with or without preceding exacerbation of the angina pectoris. As with other beta blockers, when discontinuation of TENORMIN is planned, the patients should be carefully observed and advised to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommended that TENORMIN be promptly reinstituted, at least temporarily. (See DOSAGE AND ADMINISTRATION.)

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is not absolute, the lowest possible dose of TENORMIN should be used with therapy initiated at 50 mg and a beta$_2$-stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: It is not advisable to withdraw beta-adrenoreceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using anesthetic agents such as ether, cyclopropane, and trichloroethylene. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg IV).

Additionally, caution should be used when TENORMIN I.V. Injection is administered concomitantly with such agents.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents: eg, dobutamine or isoproterenol with caution.

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. At recommended doses TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely. (See DOSAGE AND ADMINISTRATION.)

PRECAUTIONS: General: Patients already on a beta blocker must be evaluated carefully before TENORMIN is administered. Initial and subsequent TENORMIN dosages can be adjusted downward depending on clinical observations including pulse and blood pressure.

Impaired Renal Function: The drug should be used with caution in patients with impaired renal function. (See DOSAGE AND ADMINISTRATION.)

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Information on concurrent usage of atenolol and aspirin is limited. Data from several studies, ie, TIMI-II, ISIS-2, currently do not suggest any clinical interaction between aspirin and beta blockers in the acute myocardial infarction setting.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human antihypertensive dose,* did not indicate a carcinogenic potential of atenolol. A third (24 month) rat study, employing doses of 500 and 1,500 mg/kg/day (250 and 750 times the maximum recommended human antihypertensive dose*) resulted in increased incidences of benign adrenal medullary tumors in males and females, mammary fibroadenomas in females, and anterior pituitary adenomas and thyroid para-follicular cell carcinomas in males. No evidence of a mutagenic potential of atenolol was uncovered in the dominant lethal test (mouse), in vivo cytogenetics test (Chinese hamster) or Ames test (*S typhimurium*.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose*) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies employing oral atenolol performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human antihypertensive dose*) and increased incidence of atrial degeneration of hearts of male rats at 300 but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human antihypertensive dose,* respectively).

Usage in Pregnancy: Pregnancy Category C: Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human antihypertensive dose.* Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg/day or 12.5 times the maximum recommended human antihypertensive dose.* There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Based on the maximum dose of 100 mg/day in a 50 kg patient weight.

Nursing Mothers: Atenolol is excreted in human breast milk at a ratio of 1.5 to 6.8 when compared to the concentration in plasma. Caution should be exercised when TENORMIN is administered to a nursing woman. Clinically significant bradycardia has been reported in breast fed infants. Premature infants, or infants with impaired renal function, may be more likely to develop adverse effects.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient.

Frequency estimates were derived from controlled studies in hypertensive patients in which adverse reactions were either volunteered by the patient (US studies) or elicited, eg, by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects of TENORMIN and placebo is similar, causal relationship to TENORMIN is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the US studies (volunteered side effects) and then from both US and foreign studies (volunteered and elicited side effects):

US STUDIES (ATENOLOL, n=164; PLACEBO, n=206) (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%)

CENTRAL NERVOUS SYSTEM/ NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%)

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%)

RESPIRATORY (see WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%)

TOTALS US AND FOREIGN STUDIES (ATENOLOL, n=399; PLACEBO, n=407):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)

CENTRAL NERVOUS SYSTEM/ NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%)

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%)

Acute Myocardial Infarction: In a series of investigations in the treatment of acute myocardial infarction, bradycardia and hypotension occurred more commonly, as expected for any beta blocker, in atenolol-treated patients than in control patients. However, these usually responded to atropine and/or to withholding further dosage of atenolol. The incidence of heart failure was not increased by atenolol. Inotropic agents were infrequently used. The reported frequency of these and other events occurring during these investigations is given below.

In a study of 477 patients, the following adverse events were reported during either intravenous and/or oral atenolol administration:

CONVENTIONAL THERAPY PLUS ATENOLOL (n=244): bradycardia, 43 (18%); hypotension, 60 (25%); bronchospasm, 3 (1.2%); heart failure, 46 (19%); heart block, 11 (4.5%); BBB + major axis deviation, 16 (6.6%); supraventricular tachycardia, 28 (11.5%); atrial fibrillation, 12 (5%); atrial flutter, 4 (1.6%); ventricular tachycardia, 39 (16%); cardiac reinfarction, 0 (0%); total cardiac arrests, 4 (1.6%); nonfatal cardiac arrests, 4 (1.6%); deaths, 7 (2.9%); cardiogenic shock, 1 (0.4%); development of ventricular septal defect, 0 (0%); development of mitral regurgitation, 0 (0%); renal failure, 1 (0.4%); pulmonary emboli, 3 (1.2%)

CONVENTIONAL THERAPY ALONE (n=233): bradycardia, 24 (10%); hypotension, 34 (15%); bronchospasm, 2 (0.9%); heart failure, 56 (24%); heart block, 10 (4.3%); BBB + major axis deviation, 28 (12%); supraventricular tachycardia, 45 (19%); atrial fibrillation, 29 (11%); atrial flutter, 7 (3%); ventricular tachycardia, 52 (22%); cardiac reinfarction, 6 (2.6%); total cardiac arrests, 16 (6.9%); nonfatal cardiac arrests, 12 (5.1%); deaths, 16 (6.9%); cardiogenic shock, 4 (1.7%); development of ventricular septal defect, 2 (0.9%); development of mitral regurgitation, 2 (0.9%); renal failure, 0 (0%); pulmonary emboli, 0 (0%)

In the subsequent International Study of Infarct Survival (ISIS-1) including over 16,000 patients of whom 8,037 were randomized to receive TENORMIN treatment, the dosage of intravenous and subsequent oral TENORMIN was either discontinued or reduced for the following reasons:

	Reasons for Reduced Dosage IV Atenolol Reduced Dose (< 5 mg)*		Oral Partial Dose	
Hypotension/Bradycardia	105	(1.3%)	1168	(14.5%)
Cardiogenic Shock	4	(.04%)	35	(.44%)
Reinfarction	0	(0%)	5	(.06%)
Cardiac Arrest	5	(.06%)	28	(.34%)
Heart Block (> first degree)	5	(.06%)	143	(1.7%)
Cardiac Failure	1	(.01%)	233	(2.9%)
Arrhythmias	3	(.04%)	22	(.27%)
Bronchospasm	1	(.01%)	50	(.62%)

*Full dosage was 10 mg and some patients received less than 10 mg but more than 5 mg.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN.

Hematologic: Agranulocytosis, purpura.

Allergic: Fever, combined with aching and sore throat, laryngospasm, and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances: hallucinations; an acute reversible syndrome characterized by disorientation of time and place; short-term memory loss; emotional lability with slightly clouded sensorium; and, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small, and in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy. (See DOSAGE AND ADMINISTRATION.)

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

During postmarketing experience with TENORMIN, the following have been reported in temporal relationship to the use of the drug: reversible alopecia, impotence, elevated liver enzymes and or bilirubin, and thrombocytopenia.

DOSAGE AND ADMINISTRATION: Hypertension: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Angina Pectoris: The initial dose of TENORMIN is 50 mg given as one tablet a day. If an optimal response is not achieved within one week, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Some patients may require a dosage of 200 mg once a day for optimal effect.

Twenty-four hour control with once daily dosing is achieved by giving doses larger than necessary to achieve an immediate maximum effect. The maximum early effect on exercise tolerance occurs with doses of 50 to 100 mg, but at these doses the effect at 24 hours is attenuated, averaging about 50% to 75% of that observed with once a day oral doses of 200 mg.

Acute Myocardial Infarction: In patients with definite or suspected acute myocardial infarction, treatment with TENORMIN I.V. Injection should be initiated as soon as possible after the patient's arrival in the hospital and after eligibility is established. Such treatment should be initiated in a coronary care or similar unit immediately after the patient's hemodynamic condition has stabilized. Treatment should begin with the intravenous administration of 5 mg TENORMIN over 5 minutes followed by another 5 mg intravenous injection 10 minutes later. TENORMIN I.V. Injection should be administered under carefully controlled conditions including monitoring of blood pressure, heart rate, and electrocardiogram. Dilutions of TENORMIN I.V. Injection in Dextrose Injection USP, Sodium Chloride Injection USP, or Sodium Chloride and Dextrose Injection may be used. These admixtures are stable for 48 hours if they are not used immediately.

In patients who tolerate the full intravenous dose (10 mg), TENORMIN Tablets 50 mg should be initiated 10 minutes after the last intravenous dose followed by another 50 mg oral dose 12 hours later. Thereafter, TENORMIN can be given orally either 100 mg once daily or 50 mg twice a day for a further 6-9 days or until discharge from the hospital. If bradycardia or hypotension requiring treatment or any other untoward effects occur, TENORMIN should be discontinued. (See full prescribing information prior to initiating therapy with TENORMIN Tablets.)

Data from other beta blocker trials suggest that if there is any question concerning the use of IV beta blocker or clinical estimate that there is a contraindication, the IV beta blocker may be eliminated and patients fulfilling the safety criteria may be given TENORMIN Tablets 50 mg twice daily or 100 mg once a day for at least seven days (if the IV dosing is excluded).

Although the demonstration of efficacy of TENORMIN is based entirely on data from the first seven postinfarction days, data from other beta blocker trials suggest that treatment with beta blockers that are effective in the postinfarction setting may be continued for one to three years if there are no contraindications.

TENORMIN is an additional treatment to standard coronary care unit therapy.

Patients with Renal Impairment: Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 mL/min/1.73m^2 (normal range is 100-150 mL/min/1.73m^2); therefore, the following maximum oral dosages are recommended for patients with renal impairment.

Creatinine Clearance (mL/min/1.73m^2)	Atenolol Elimination Half-Life (h)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

Cessation of Therapy in Patients with Angina Pectoris: If withdrawal of TENORMIN therapy is planned, it should be achieved gradually and patients should be carefully observed and advised to limit physical activity to a minimum.

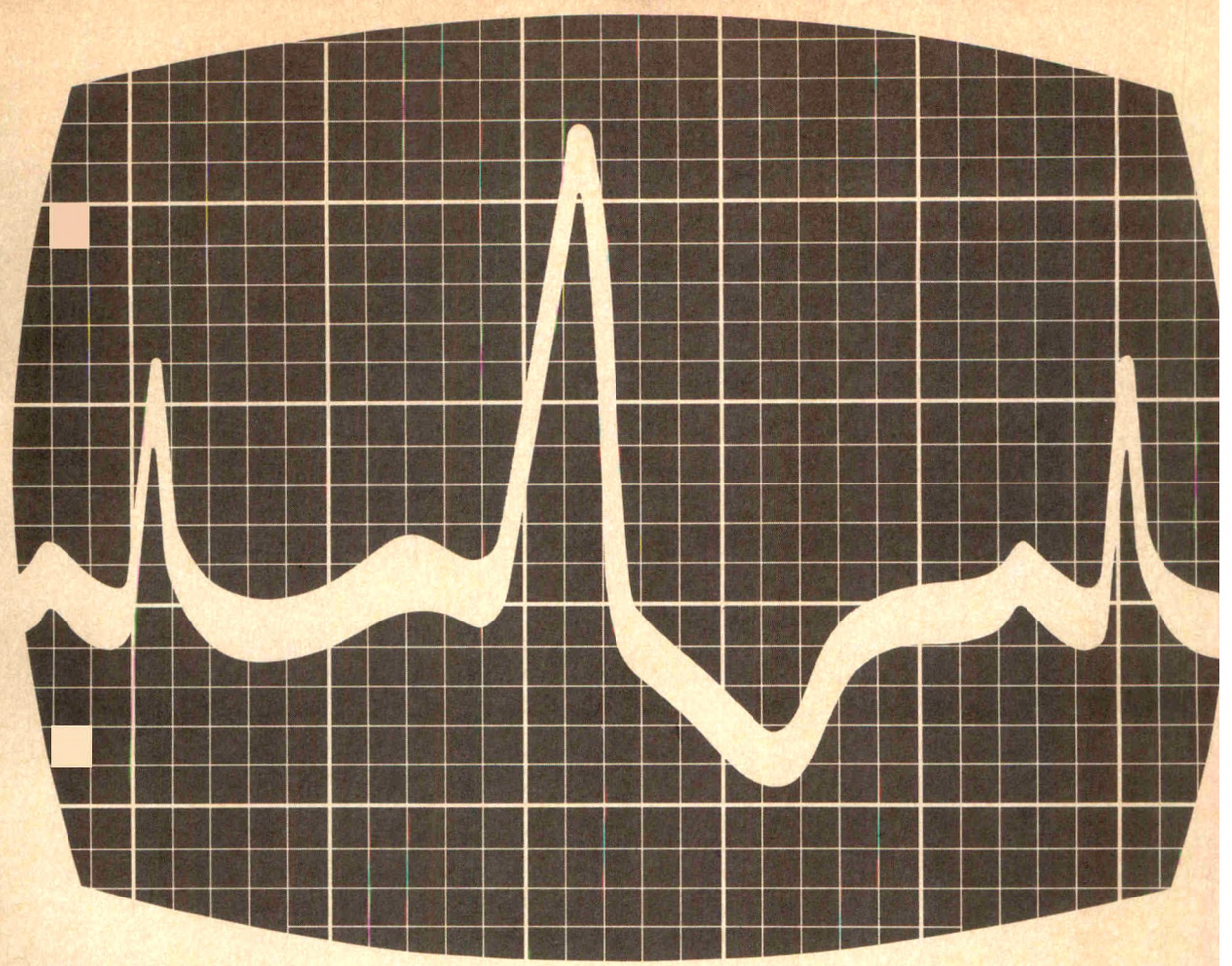
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Rev N 03/90

References: 1. ISIS-1 (First International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous atenolol among 16,027 cases of suspected acute myocardial infarction: ISIS-1. *Lancet.* 1986;2:57-66. **2.** TENORMIN Professional Information Brochure.

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PVC OR P.C.P.?

(Angel Dust)

The physiological and psychological symptoms of substance abuse can mimic an astounding range of systemic disorders.

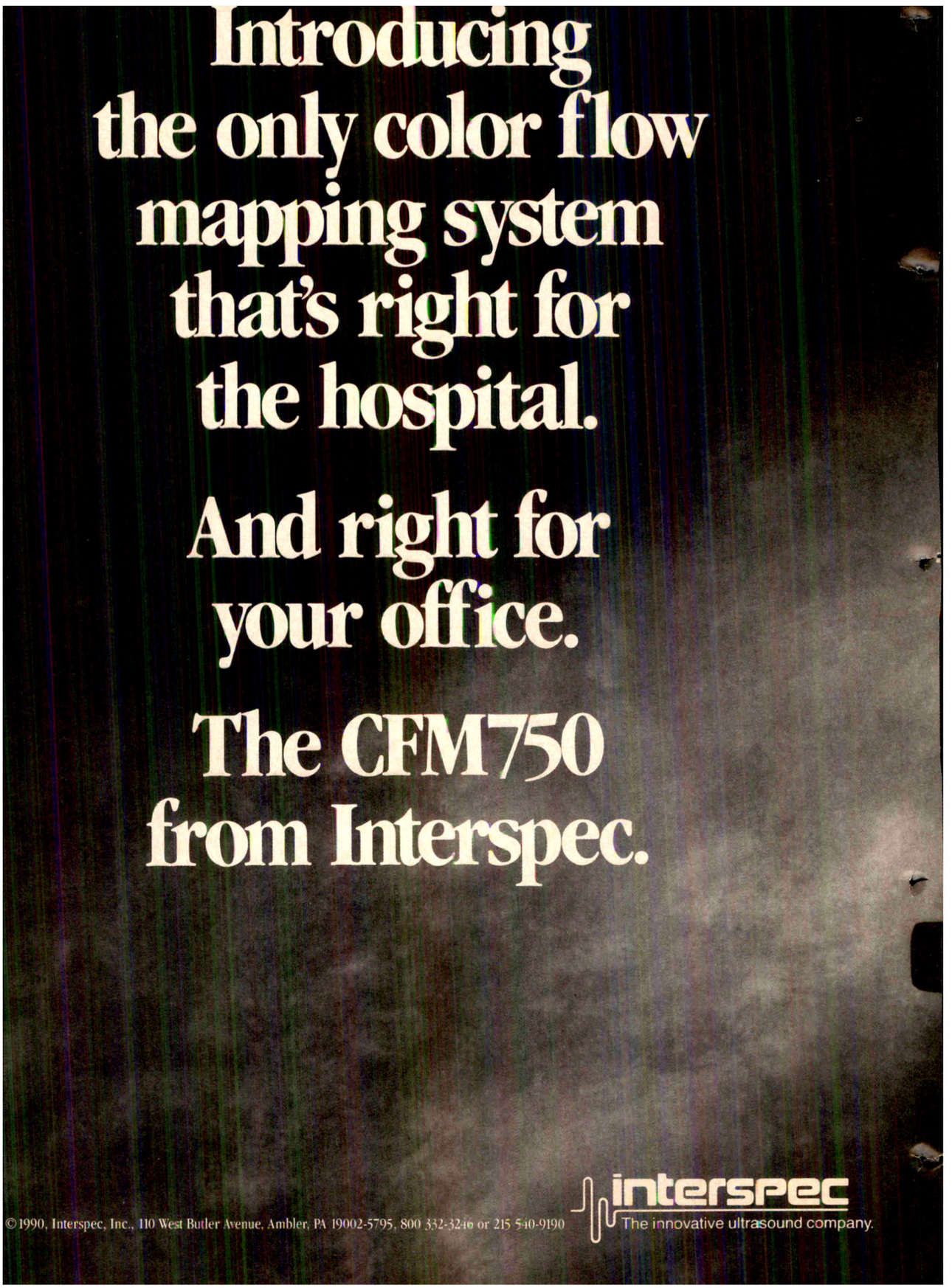
Even more frightening is the fact that illegal drugs can cause sudden death *before* any symptoms occur – regardless of the dose, blood levels, or route of administration.

Help your patients stop illegal drug use before it stops them. Ask about abuse as a routine part of your examination.

For information, healthcare professionals may call the National Clearinghouse for Alcohol and Drug Abuse: 1-301-468-2600, Monday through Friday, 8:30 AM – 4:30 PM EST.

HELP STOP SUBSTANCE ABUSE.
ASK THE QUESTIONS.

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Until now, proven hospital-quality color flow mapping just wasn't available for your office. Interspec has changed all that with the CFM750–at a size and price that are right for your practice.

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The compact, easily moveable CFM750 is the ideal unit for adult cardiology, pediatric, and neonatal studies. It has special features such as the only TEE probe with fully steerable CW, pulsed, and high-PRF Doppler. It can be interfaced with a wide choice of stress echo systems. And advanced research capabilities let you connect the CFM750 to an Apple® Macintosh® II.

The CFM750 will grow with you. It's software-driven, so upgrades and enhancements are simple and affordable. And it's all from Interspec, a world leader in the development of outstanding cardiovascular ultrasound systems.

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See the CFM750 at AHA, Booth No. 1066.

CFM 750

CONGESTIVE HEART FAILURE

1107
Comparison of Intravenous Amrinone and Dobutamine in Congestive Heart Failure Due to Idiopathic Dilated Cardiomyopathy

Richard H. Marcus, Keith Raw, Jay Patel, Abdul Mitha, and Pinhas Sareli

In a randomized study, the hemodynamic responses to 48-hour infusions of amrinone or dobutamine were compared in 46 patients with dilated cardiomyopathy and heart failure unresponsive to oral medication. Although both agents were found to be effective and safe forms of short-term parenteral therapy in these patients, some important differences were noted. There were fewer nonresponders with amrinone. Amrinone produced a more consistent diuretic effect, but also caused tachycardia, which was not observed with dobutamine. The effective dose of amrinone was more predictable than that of dobutamine.

1113
Comparison of Frequency of Late Potentials in Idiopathic Dilated Cardiomyopathy and Ischemic Cardiomyopathy with Advanced Congestive Heart Failure and Their Usefulness in Predicting Sudden Death

Holly R. Middlekauff, William G. Stevenson, Mary A. Woo, Debra K. Moser, and Lynne Warner Stevenson

Signal-averaged electrocardiograms were obtained in 62 consecutive patients with advanced congestive heart failure (CHF). Late potentials were present in 16 of 40 (40%) patients with old infarction but in only 3 of 22 (14%) patients with nonischemic CHF ($p = 0.03$). Late potentials were not associated with more severe ventricular ectopic activity on 24-hour ambulatory electrocardiograms. At 1 year, the actuarial sudden death risk was 12% in patients with late potentials versus 21% in those without ($p = 0.73$). Thus, late potentials are more common when CHF is due to old myocardial infarction. The signal-averaged electrocardiogram and ambulatory electrocardiogram provide independent information and do not identify the same CHF patients. However, late potentials are poor predictors of sudden death risk when CHF is advanced, possibly due to the heterogeneity of causes of sudden death.

1118
Value of Carvedilol in Congestive Heart Failure Secondary to Coronary Artery Disease

Prabir Das Gupta, Paul Broadhurst, Edward B. Raftery, and Avijit Lahiri

A preliminary, open study was carried out to elucidate the effects of β blockade in chronic heart failure. Twelve patients with chronic heart failure secondary to ischemic heart disease were treated for 8 weeks with carvedilol, a new vasodilating β blocker with balanced α-blocking properties. Exercise capacity, hemodynamics and left ventricular ejection fraction were measured before and after 8 weeks of carvedilol therapy (12.5 mg to 50 mg twice a day). Exercise capacity, resting ejection fraction and stroke volume index increased significantly, along with a decrease in

Continued on page A43

A BRIGHT IDEA... IN MILD TO MODERATE HYPERTENSION

180-mg Calan SR...once-daily, single-agent therapy

- Efficacy proven comparable to 240 mg[1]
- 24-hour control with once-daily dosing[1]*
- Low-dose, well-tolerated† therapy[1]

A more economical choice‡



ONCE DAILY **180 mg**

Calan® SR

verapamil HCl 180 mg

SUSTAINED-RELEASE **CAPLETS**

*Total daily dosages above 240 mg should be administered in divided doses. Calan SR should be administered with food.

†Constipation, which is easily managed in most patients, is the most commonly reported side effect of Calan SR.

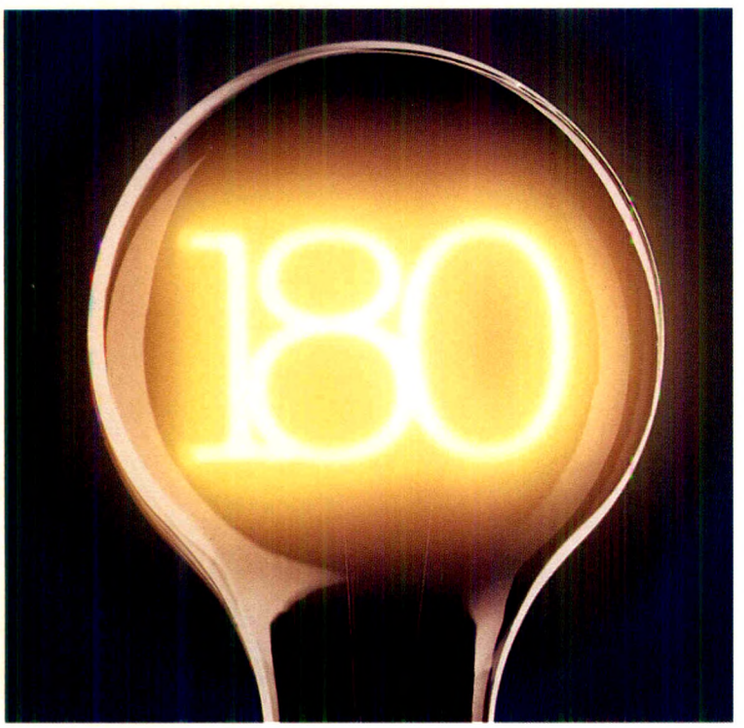
‡Price comparison versus 240-mg Calan SR.

Please see next page of this advertisement for references and a brief summary of prescribing information.

SEA

Consistent with 1988 JNC recommendation...

The 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure recommends that blood pressure be controlled "...with the fewest drugs at their lowest dose...."[2]



When you want high single-agent efficacy in a lower dose, prescribe...

ONCE DAILY **180 mg**

Calan® SR

verapamil HCl 180 mg

SUSTAINED-RELEASE CAPLETS

A BRIGHT IDEA
in verapamil SR therapy

References:

1. Data on file, G.D. Searle & Co. **2.** 1988 Joint National Committee: The 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1988;148:1023-1038.

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, increased urination, spotty menstruation, impotence.

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A90CA4511T

pulmonary capillary wedge pressure, systemic vascular resistance, rest and exercise heart rate and blood pressure. Exercise ejection fraction and cardiac index did not show any significant change. These preliminary results suggest that carvedilol may be of benefit in chronic heart failure and that further, controlled studies are indicated.

VALVULAR HEART DISEASE

1124
Improvement in Early Diastolic Filling Dynamics After Aortic Valve Replacement

Ian C. Gilchrist, Harvey L. Waxman, and Peter B. Kurnik

With use of ultrafast computed tomography, 13 patients undergoing aortic valve surgery for aortic stenosis were prospectively followed to evaluate the relation between left ventricular mass and diastolic function. Mass decreased from 161 ± 11 g/m^2 (± standard error of the mean) at baseline to 106 ± 5 g/m^2, and then to 97 ± 7 g/m^2 postoperatively at 4 and 8 months, respectively, in 12 patients who demonstrated significant (>20%) mass regression. Diastolic function, defined by the peak filling rate of early diastole, improved ($p < 0.02$) in the group with mass regression, from 2.11 ± 0.17 s^{-1} at baseline to 2.12 ± 0.23 s^{-1}, and then to 2.62 ± 0.26 s^{-1} at 4 and 8 months, respectively. Improvement in diastolic function correlated with a reduction in ventricular mass. Thus, improvement in diastolic function can be seen after aortic valve surgery but follows the regression in wall mass.

MISCELLANEOUS

1131
Lipoprotein and Hepatic Lipase Activity and High-Density Lipoprotein Subclasses After Cardiac Transplantation

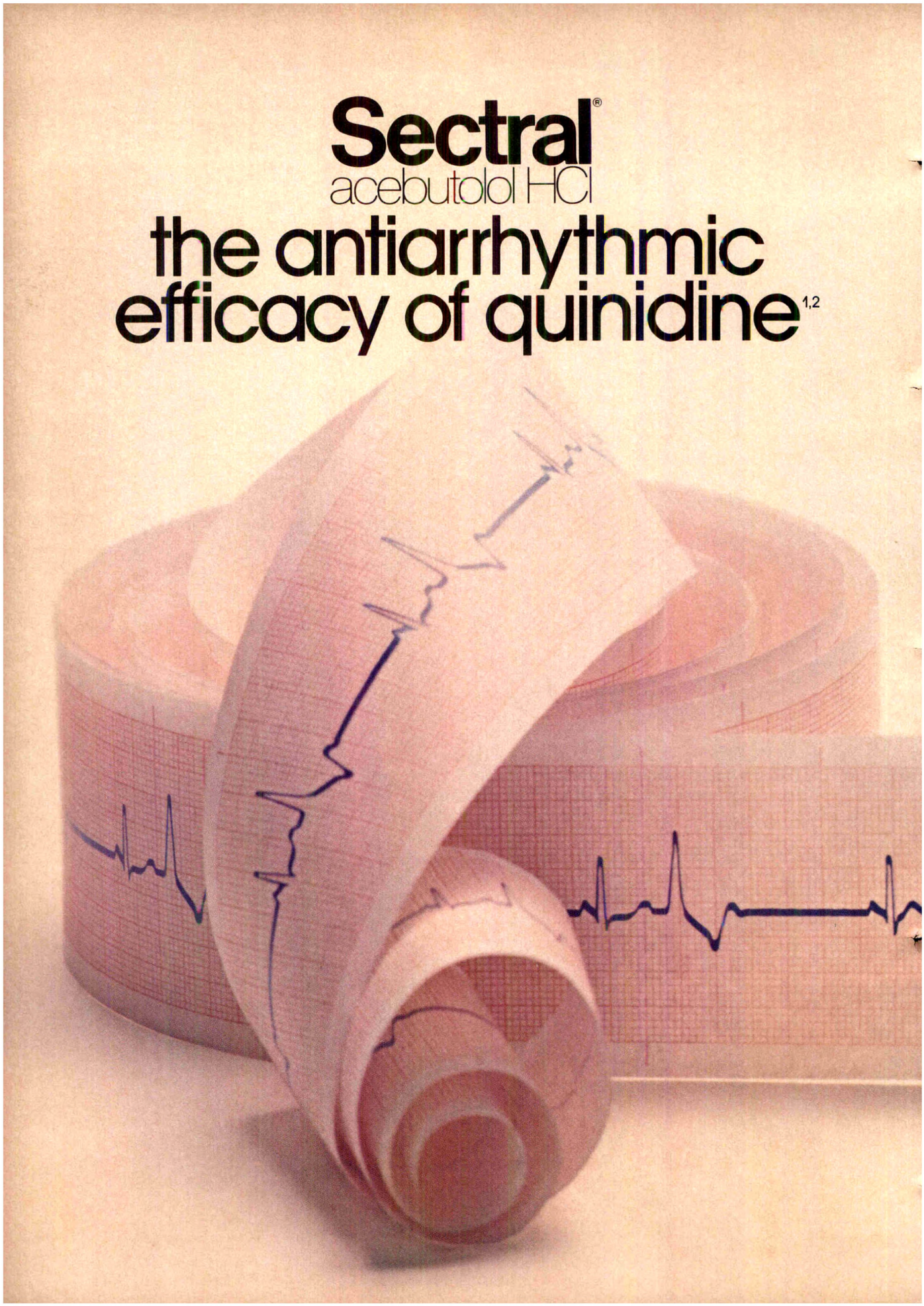
H. Robert Superko, William L. Haskell, and Connie D. Di Ricco

The interaction of immunosuppressive medications with plasma triglycerides, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, HDL_2 and HDL_3 cholesterol, and hepatic and lipoprotein lipase activity in 72 cardiac transplant patients and 51 control subjects was investigated. Greater concentrations of plasma triglyceride ($p < 0.001$) and LDL cholesterol ($p < 0.005$) and greater hepatic lipase activity ($p < 0.001$) were noted in the transplant patients, whereas lipoprotein lipase activity was significantly lower ($p < 0.001$). No difference was detected in HDL, HDL_2 or HDL_3 cholesterol. Cyclosporine dose was significantly associated with hepatic lipase activity ($p < 0.02$), inversely associated with lipoprotein lipase activity ($p < 0.05$) and was the major source of variation in hepatic lipase activity.

Continued on page A47

Sectral®
acebutolol HCl

the antiarrhythmic efficacy of quinidine[1,2]



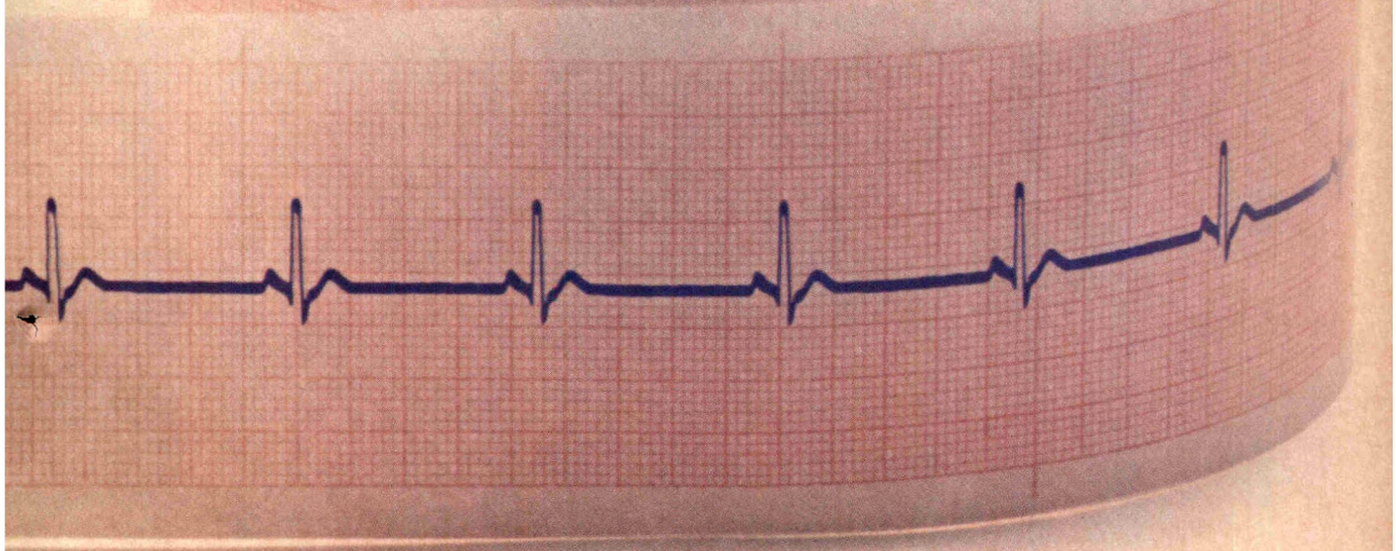
...and the safety of a beta blocker.

Sectral® (acebutolol HCl) is a beta blocker demonstrated as effective as quinidine in a wide range of premature ventricular complexes (paired and multiform ventricular ectopic beats and R-on-T beats).* Sectral® offers excellent G.I. tolerability. It does not interact with digoxin. And Sectral, like other beta blockers, is rarely associated with proarrhythmia.[3]

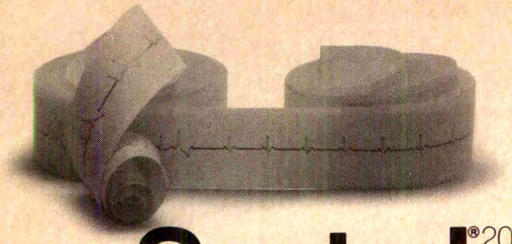
Initiate Sectral therapy with 200 mg b.i.d. Dosage can be increased gradually until optimal response is obtained, generally between 600 mg to 1200 mg per day.

*Sectral® is not indicated for ventricular tachycardia.
Please see brief summary on adjacent page.

Like other beta blockers, Sectral® is contraindicated in persistently severe bradycardia, second- and third-degree heart block, overt cardiac failure or cardiogenic shock.



Sectral®
acebutolol HCl
For uncomplicated control of PVCs.



Sectral® 200 mg 400 mg CAPSULES
acebutolol HCl

For uncomplicated control of PVCs.

(Brief Summary. See Package Circular for full prescribing information.)

CONTRAINDICATIONS: SECTRAL is contraindicated in: 1) persistently severe bradycardia; 2) second- and third-degree heart block; 3) overt cardiac failure; 4) cardiogenic shock. (See WARNINGS)

WARNINGS: Cardiac Failure: Sympathetic stimulation may be essential for support of circulation in patients with diminished myocardial contractility, and inhibition by β-adrenergic receptor blockade may precipitate more severe failure. Although β-blockers should be avoided in overt cardiac failure, SECTRAL can be used cautiously when heart failure is controlled with digitalis and/or diuretics. Digitalis and SECTRAL impair AV conduction. Withdraw SECTRAL if cardiac failure persists.

In Patients Without a History of Cardiac Failure: In patients with aortic or mitral valve disease or compromised left ventricular function, continued depression of the myocardium with β-blockers over time may lead to cardiac failure. Digitalize patients at first signs of failure, and/or give a diuretic and observe closely. Withdraw SECTRAL if cardiac failure persists.

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Abrupt discontinuation of some β-blockers in coronary artery disease patients may exacerbate angina; in some cases, myocardial infarction and death have been reported. Caution such patients against interruption of therapy without a physician's advice. Even in the absence of overt ischemic heart disease, withdraw SECTRAL gradually over a period of about two weeks; observe carefully and advise patients to minimize physical activity during this time (If desired, patients may be transferred directly to comparable doses of an alternative β-blocker without interruption of β-blocking therapy). If exacerbation of angina occurs, restart full-dose anti-anginal therapy immediately and hospitalize patient until stabilized.

Peripheral Vascular Disease: β-antagonists reduce cardiac output and can precipitate/aggravate arterial insufficiency in patients with peripheral or mesenteric vascular disease. Exercise caution and observe such patients closely for progression of arterial obstruction.

Bronchospastic Diseases: Patients with Bronchospastic Disease Should, in General, Not Receive a β-Blocker. Because of its relative β -selectivity, low doses of SECTRAL may be used cautiously in such patients who do not respond to, or cannot tolerate, alternative treatment.

Since β_1-selectivity is not absolute and is dose-dependent, use lowest possible dose of SECTRAL initially, preferably in divided doses. Make bronchodilator, e.g. theophylline, or a β_2-stimulant, available in advance with instructions for use.

Anesthesia and Major Surgery: The necessity/desirability of withdrawing β-blockers prior to major surgery is controversial; the heart's impaired ability to respond to β-adrenergically mediated reflex stimuli may enhance the risk of excessive myocardial depression during general anesthesia. Difficulty in restarting and maintaining the heartbeat also has been reported with beta-blockers. If treatment is continued take special care when using anesthetics that depress the myocardium; use lowest possible SECTRAL dose. SECTRAL, like other β-blockers, is a competitive inhibitor of β-receptor agonists, so its effects can be reversed by cautious administration of such agents (e.g., dobutamine or isoproterenol). Symptoms of excessive vagal tone (e.g., profound bradycardia, hypotension) may be corrected with atropine.

Diabetes and Hypoglycemia: β-blockers may potentiate insulin-induced hypoglycemia and mask some symptoms such as tachycardia; dizziness and sweating are usually not significantly affected. Warn diabetics of possible masked hypoglycemia.

Thyrotoxicosis: β-adrenergic blockade may mask some clinical signs (tachycardia) of hyperthyroidism. Abrupt withdrawal of SECTRAL may precipitate a thyroid storm in patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal or Hepatic Function: While there are no U.S. studies, foreign published experience shows that acebutolol has been used successfully in chronic renal insufficiency. Acebutolol is excreted via the G.I. tract, but the active metabolite, diacetolol, is eliminated mainly by the kidney. A linear relationship exists between renal clearance of diacetolol and creatinine clearance (Cl_{cr}); reduce daily dose of acebutolol by 50% when Cl_{cr} is less than 50 mL/min and by 75% when it is less than 25 mL/min. Use cautiously in patients with impaired hepatic function.

SECTRAL has been used successfully and without problems in elderly patients in U.S. clinical trials without specific dosage adjustment. However, in the elderly, lower maintenance doses may be required because bioavailability of SECTRAL and its metabolite are approximately doubled.

Information for Patients: Warn patients, especially those with evidence of coronary artery disease, against interruption or discontinuation of SECTRAL without physician supervision. Although cardiac failure rarely occurs in proper y selected patients, advise patients to consult a physician if signs or symptoms suggestive of impending CHF, or unexplained respiratory symptoms, develop.

Warn patients of possible severe hypertensive reactions from concomitant use of α-adrenergic stimulants, e.g., nasal decongestants used in OTC cold medicines and nasal drops.

Clinical Laboratory Findings: SECTRAL, like other β-blockers, has been associated with development of antinuclear antibodies (ANA). In prospective clinical trials, patients receiving SECTRAL had a dose-dependent increase in the development of positive ANA titers. Symptoms related to this laboratory abnormality were infrequent. Symptoms and ANA titers were reversible upon discontinuation of SECTRAL.

Drug Interactions: Catecholamine-depleting drugs may have additive effects when given with β-blockers. Observe patients treated with both agents closely for evidence of marked bradycardia or hypotension which may present as vertigo, syncope/presyncope, or orthostatic changes in blood pressure without compensatory tachycardia. Exaggerated hypertensive responses have been reported from use of β-adrenergic antagonists with α-adrenergic stimulants, including those in OTC cold remedies and vasoconstrictive nasal drops. Nonsteroidal anti-inflammatory drugs may blunt antihypertensive effects of beta-blockers.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies in rats and mice, at doses 15 times the maximum recommended (60 kg) human dose, did not indicate carcinogenic potential for SECTRAL. Diacetolol, the major metabolite in man, was without carcinogenic potential in rats at doses up to 1800 mg/kg/d. SECTRAL and diacetolol also had no mutagenic potential in the Ames Test. No significant impact on reproductive performance or fertility was found in rats following SECTRAL or diacetolol doses of up to 240 or 1000 mg/kg/d, respectively.

Pregnancy: *Teratogenic Effects:* Pregnancy Category B. No teratogenic effects were seen in rat or rabbit reproduction studies utilizing SECTRAL doses that were, respectively, approximately 31.5 and 6.8 times the maximum recommended human dose. At this dose in the rabbit, slight fetal growth retardation was noted; this was considered to be a result of maternal toxicity (evidenced by reduced food intake, lowered rate of body weight gain, mortality). Diacetolol studies (doses up to 450 mg/kg/d in rabbits and up to 1800 mg/kg/d in rats) showed no evidence of fetal harm other than a significant elevation in postimplantation loss with 450 mg/kg/d, a level at which food consumption and body weight gain were reduced in rabbit dams; there was a non-statistically significant increase in incidence of bilateral cataract in rat fetuses from dams treated with 1800 mg/kg/d. There are no adequate and well-controlled trials in pregnant women; SECTRAL should be used during pregnancy only if potential benefit justifies risk to the fetus.

Nonteratogenic Effects: Human studies indicate that acebutolol and diacetolol cross the placenta. Neonates of mothers who received acebutolol during pregnancy have reduced birth weight, decreased blood pressure, and decreased heart rate.

Labor and Delivery: Effect on labor and delivery in pregnant women is unknown. Animal studies have shown no effect of SECTRAL on the usual course of labor and delivery.

Nursing Mothers: Acebutolol and diacetolol appear in breast milk (milk:plasma ratio of 7.1 and 12.2, respectively). Use in nursing mothers is not recommended.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: SECTRAL is well tolerated in properly selected patients. Most adverse effects have been mild, not required therapy discontinuation, and tended to decrease as treatment duration increases.

The incidence of treatment-related side effects (volunteered and elicited) derived from U.S. controlled clinical trials in patients with hypertension, angina and arrhythmia follows. Numbers represent percentage incidence for SECTRAL (N = 1002) versus placebo (N = 314), respectively.

Cardiovascular: Chest pain 2%, 1%; Edema 2%, 1%. *CNS:* Depression 2%, 1%; Dizziness 6%, 2%; Fatigue 11%, 4%; Headache 6%, 4%; Insomnia 3%, 1%. Abnormal dreams 2%, 1%. *Dermatologic:* Rash 2%, 1%. *Gastrointestinal:* Constipation 4%, 0%; Diarrhea 4%, 1%; Dyspepsia 4%, 1%; Flatulence 3%, 1%; Nausea 4%, 0%. *Genitourinary:* Micturition (frequency) 3%, <1%. *Musculoskeletal:* Arthralgia 2%, 2%. Myalgia 2%, 0%. *Respiratory:* Cough 1%, 0%; Dyspnea 4%, 2%; Rhinitis 2%, <1%. *Special Senses:* Abnormal Vision 2%, 0%.

The following selected (potentially important) side effects were seen in up to 2% of SECTRAL patients: *Cardiovascular:* hypotension, bradycardia, heart failure. *CNS:* anxiety, hyper/hypoesthesia, impotence. *Skin:* pruritus. *Gastrointestinal:* vomiting, abdominal pain. *Genitourinary:* dysuria, nocturia. *Liver and Biliary:* small number of reported cases of liver abnormalities (increased SGOT, SGPT, LDH). In some cases, increased bilirubin or alkaline phosphatase, fever, malaise, dark urine, anorexia, nausea, headache, and/or other symptoms have been reported. In some cases, symptoms and signs were confirmed by rechallenge. Abnormalities were reversible upon drug cessation. *Musculoskeletal:* back and joint pain. *Respiratory:* pharyngitis, wheezing. *Special Senses:* conjunctivitis, dry eye, eye pain. *Autoimmune:* extremely rare reports of systemic lupus erythematosis.

Incidence of drug-related adverse effects (volunteered and solicited) based on SECTRAL dose is shown below. (Data from 266 hypertensive patients treated for 3 months on a constant dose.)

Body System	400 mg/day (N = 132)	800 mg/day (N = 63)	1200 mg/day (N = 71)
Cardiovascular	5%	2%	1%
Gastrointestinal	3%	3%	7%
Musculoskeletal	2%	3%	4%
Central Nervous System	9%	13%	17%
Respiratory	1%	5%	6%
Skin	1%	2%	1%
Special Senses	2%	2%	6%
Genitourinary	2%	3%	1%

Potential Adverse Effects: Certain adverse effects not listed above have been reported with other β-blocking agents and should be considered as potential adverse effects of SECTRAL.

CNS: Reversible mental depression progressing to catatonia, an acute syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS).

Allergic: Erythematous rash, fever with aching and sore throat, laryngospasm, respiratory distress.

Hematologic: Agranulocytosis, nonthrombocytopenic and thrombocytopenic purpura.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Misc.: Reversible alopecia, Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with SECTRAL.

Keep at room temperature. Approximately 25°C (77°F).

3482-5 6/21/89

WYETH-AYERST LABORATORIES
Philadelphia, PA 19101

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1135
Serial Evaluation of Lipid Profiles and Risk Factors for Development of Hyperlipidemia After Cardiac Transplantation
Laszlo Rudas, Peter W. Pflugfelder, F. Neil McKenzie, Alan H. Menkis, Richard J. Novick, and William J. Kostuk

At 1 year after heart transplantation, 83% of patients had serum cholesterol levels >5.2 mmol/liter (200 mg/dl) and 28% of patients had serum cholesterol higher than the age- and sex-matched 95th percentile. Serum cholesterol correlated with the recipient age, preoperative cholesterol level, the actual dose of maintenance prednisone at 1 year and the cumulative 1-year steroid dose. Serum triglyceride level at 1 year correlated with the pretransplant level of triglycerides, recipient age and cumulative 1-year steroid dose. Patients with a pretransplant diagnosis of coronary artery disease and obesity had a significantly higher level of serum cholesterol and triglycerides at 1 year. Hyperlipidemia occurs frequently and is detected within the first month after heart transplantation.

EDITORIAL

1139
Late Proarrhythmia and Understanding the Time of Occurrence of Proarrhythmia
Harold L. Kennedy

BRIEF REPORTS

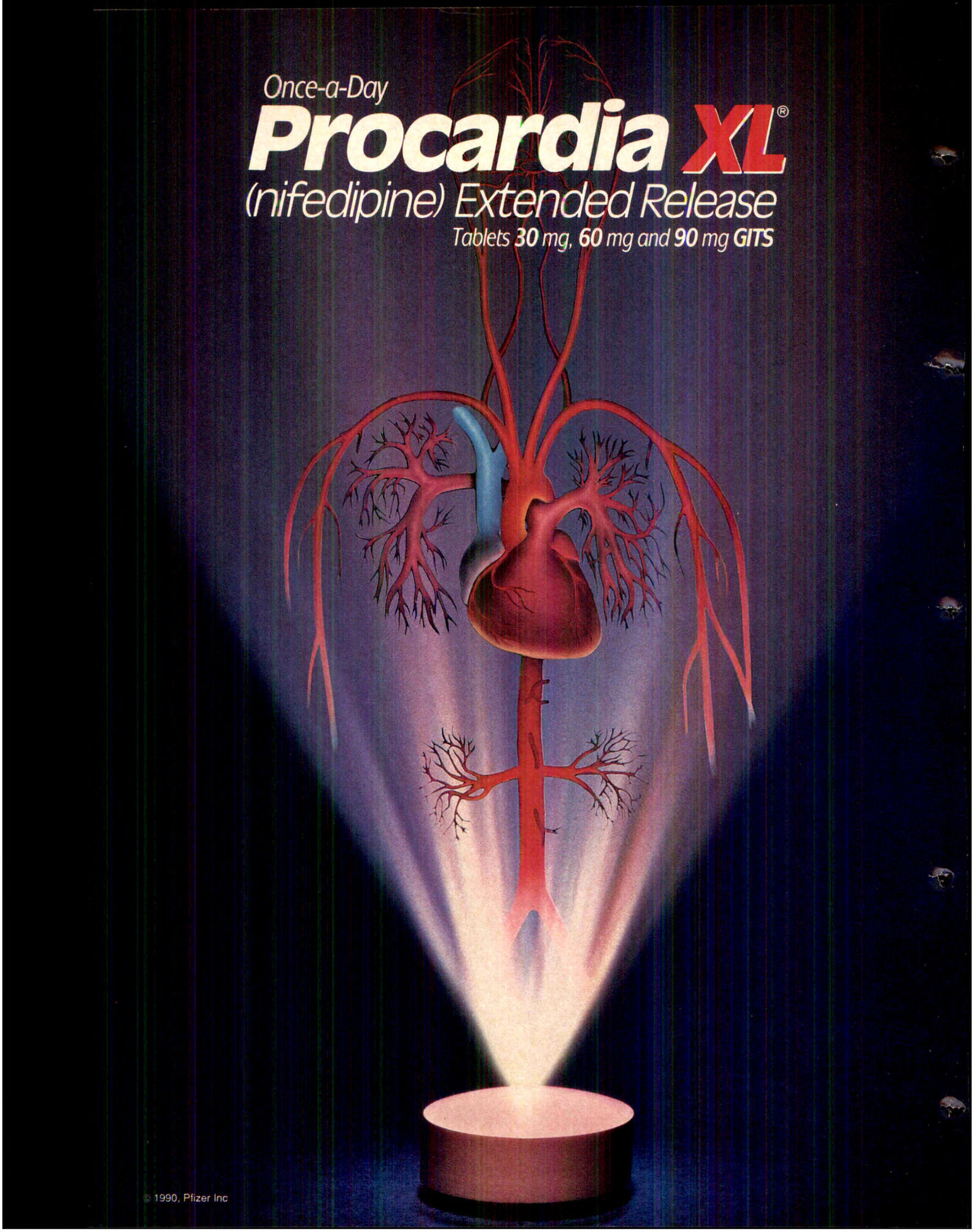
1144
Electrocardiographic Q-Wave Inconstancy in Inferior Wall Myocardial Infarction
Mei-Yu Chuang and David H. Spodick

1146
ST Elevation in the Right Chest Leads in Anterior Wall Left Ventricular Acute Myocardial Infarction
Hajime Kataoka, Akira Tamura, Shoji Yano, Koreyasu Kanzaki, and Yoshiaki Mikuriya

1147
Emergency Stenting for Refractory Acute Coronary Artery Occlusion During Coronary Angioplasty
Pim J. de Feyter, Ivan DeScheerder, Marcel van den Brand, GertJan Laarman, Harry Suryapranata, and Patrick W. Serruys

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CLASSIFIED ADVERTISING on pages A58, A64, A67


Once-a-Day
Procardia XL®
(nifedipine) Extended Release
Tablets 30 mg, 60 mg and 90 mg GITS
© 1990, Pfizer Inc

THE EMERGENCE OF A SOURCE OF 24-HOUR ANTIHYPERTENSIVE AND ANTIANGINAL PROTECTION WITH ONCE-DAILY DOSING

NOW, Once-Daily Dosing Controls Hypertension

- The only calcium channel blocker indicated for once-a-day dosing at all doses
- Effective as monotherapy[1] and in combination[2]

Once-Daily Dosing Controls Angina

- The only once-a-day calcium channel blocker for angina
- Easy to switch from nifedipine capsules to PROCARDIA XL Extended Release Tablets[3,4]
- PROCARDIA XL angina indications: Patients with proven or suspected vasospastic angina, and patients with classic effort angina who remain symptomatic despite adequate doses of beta blockers and/or nitrates or who cannot tolerate these agents

Now, a 24-Hour Controlled-Release Delivery System

- Releases nifedipine into the gastrointestinal tract at an essentially constant rate over the 24-hour period, independent of pH, with no dose dumping[5,6]
- Minimal serum fluctuations—no significant peaks, no significant troughs[5]

- Low incidence of vasodilatory side effects. The most common side effects are peripheral edema, which is not associated with fluid retention, and headache

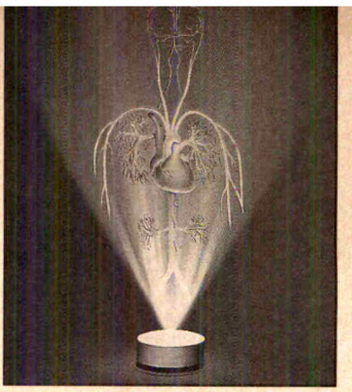
In controlled trials of 776 patients with PROCARDIA XL, edema resulted in discontinuation of therapy in 2.7% of patients[4]

Once-a-Day

Procardia XL®

(nifedipine) Extended Release

Tablets **30** mg, **60** mg and **90** mg **GITS**



24-Hour Control for Both Hypertension and Angina With Once-Daily Dosing

EASY TO INITIATE ONCE-DAILY DOSING

- Initiate once-a-day therapy with a single 30-mg or 60-mg PROCARDIA XL Extended Release Tablet, swallowed whole

EASY TO SWITCH TO ONCE-DAILY DOSING

- Over 90% of angina patients controlled on nifedipine capsules were easily switched and controlled on PROCARDIA XL Extended Release Tablets at the nearest equivalent total daily dose; others needed dosage adjustment[4]

TITRATION SHOULD PROCEED AS CLINICALLY WARRANTED

- For full dosage instructions, see prescribing information

References: 1. Gavras I, Mulinari R, Gavras H, et al: Antihypertensive effectiveness of the nifedipine gastrointestinal therapeutic system. *Am J Med* 1987;83(suppl 6B):20-23. **2.** Frishman WH, Garofalo JL, Rothschild A, et al: The nifedipine gastrointestinal therapeutic system in the treatment of hypertension. *Am J Cardiol* 1989;64(suppl to No. 11):65F-69F. **3.** Vetrovec GW, Parker VE, Cole S, et al: Nifedipine gastrointestinal therapeutic system in stable angina pectoris: Results of a multicenter open-label crossover comparison with standard nifedipine. *Am J Med* 1987;83(suppl 6B):24-29. **4.** Data on file. Medical Department, Pfizer Labs, Pfizer Inc, New York. **5.** Chung M, Reitberg DP, Gaffney M, et al: Clinical pharmacokinetics of nifedipine gastrointestinal therapeutic system: A controlled-release formulation of nifedipine. *Am J Med* 1987;83(suppl 6B):10-14. **6.** Swanson DR, Barclay BL, Wong PSL, et al: Nifedipine gastrointestinal therapeutic system. *Am J Med* 1987;83(suppl 6B):3-9.

Brief Summary
PROCARDIA XL® (nifedipine) Extended Release Tablets For Oral Use

CONTRAINDICATIONS: Known hypersensitivity reaction to nifedipine.

WARNINGS: Excessive Hypotension: Although in most angina patients the hypotensive effect of nifedipine is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving nifedipine together with a beta-blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of nifedipine and a beta blocker, but the possibility that it may occur with nifedipine alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In nifedipine-treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for nifedipine to be washed out of the body prior to surgery.

The following information should be taken into account in those patients who are being treated for hypertension as well as angina:

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting nifedipine or at the time of dosage increase. The mechanism of this effect is not established.

Beta Blocker Withdrawal: It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning nifedipine. Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of nifedipine treatment will not prevent this occurrence and on occasion has been reported to increase it.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker, have developed heart failure after beginning nifedipine. Patients with tight aortic stenosis may be at greater risk for such an event, as the unloading effect of nifedipine would be expected to be of less benefit to those patients, owing to their fixed impedance to flow across the aortic valve.

PRECAUTIONS: General—Hypotension: Because nifedipine decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of nifedipine is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.)

Peripheral Edema: Mild to moderate peripheral edema occurs in a dose dependent manner with an incidence ranging from approximately 10% to about 30% at the highest dose studied (180 mg). It is a localized phenomenon thought to be associated with vasodilation of dependent arterioles and small blood vessels and not due to left ventricular dysfunction or generalized fluid retention. With patients whose angina or hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Other: As with any other non-deformable material, caution should be used when administering PROCARDIA XL in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of PROCARDIA XL.

Laboratory Tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted. The relationship to nifedipine therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms; however, cholestasis with or without jaundice has been reported. A small (5.4%) increase in mean alkaline phosphatase was noted in patients treated with PROCARDIA XL. This was an isolated finding not associated with clinical symptoms and it rarely resulted in values which fell outside the normal range. Rare instances of allergic hepatitis have been reported. In controlled studies, PROCARDIA XL did not adversely affect serum uric acid, glucose, or cholesterol. Serum potassium was unchanged in patients receiving PROCARDIA XL in the absence of concomitant diuretic therapy, and slightly decreased in patients receiving concomitant diuretics.

Nifedipine, like other calcium channel blockers, decreases platelet aggregation *in vitro*. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some nifedipine patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for these findings has been demonstrated.

Positive direct Coombs test with/without hemolytic anemia has been reported but a causal relationship between nifedipine administration and positivity of this laboratory test, including hemolysis, could not be determined.

Although nifedipine has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to nifedipine therapy is uncertain in most cases but probable in some.

Drug Interactions—Beta-adrenergic blocking agents: (See WARNINGS) Experience in over 1400 patients with Procardia® capsules in a noncomparative clinical trial has shown that concomitant administration of nifedipine and beta-blocking agents is usually well tolerated but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angina.

Long Acting Nitrates: Nifedipine may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of nifedipine with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with corornary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing nifedipine to avoid possible over- or under-digitalization.

Coumarin Anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain.

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak nifedipine plasma levels (80%) and area-under-the-curve (74%), after a one week course of cimetidine at 1000 mg per day and nifedipine at 40 mg per day. Ranitidine produced smaller, system probably responsible for the first-pass metabolism of nifedipine. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Nifedipine was administered orally to rats, for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. Nifedipine has been shown to be teratogenic in rats when given in doses 30 times the maximum recommended human dose. Nifedipine was embryotoxic (increased fetal resorptions, decreased fetal weight, increased stunted forms, increased fetal deaths, decreased neonatal survival) in rats, mice, and rabbits at doses of from 3 to 10 times the maximum recommended human dose. In pregnant monkeys, doses 2/3 and twice the maximum recommended human dose resulted in small placentas and underdeveloped chorionic villi. In rats, doses three times maximum human dose and higher caused prolongation of pregnancy. There are no adequate and well controlled studies in pregnant women. PROCARDIA XL® (nifedipine) Extended Release Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE EXPERIENCES: Over 1000 patients from both controlled and open trials with PROCARDIA XL Extended Release Tablets in hypertension and angina were included in the evaluation of adverse experiences. All side effects reported during PROCARDIA XL Extended Release Tablet therapy were tabulated independent of their causal relation to medication. The most common side effect reported with PROCARDIA XL was edema which was dose related and ranged in frequency from approximately 10% to about 30% at the highest dose studied (180 mg). Other common adverse experiences reported in placebo-controlled trials include: headache (15.8%, compared to 9.8% placebo incidence), fatigue (5.9%, compared to 4.1% placebo incidence), dizziness (4.1%, compared to 4.5% placebo incidence), constipation (3.3%, compared to 2.3% placebo incidence), and nausea (3.3%, compared to 1.9% placebo incidence). Of these, only edema and headache were more common in PROCARDIA XL patients than placebo patients.

The following adverse reactions occurred with an incidence of less than 3.0%. With the exception of leg cramps, the incidence of these side effects was similar to that of placebo alone: *body as a whole/systemic*: asthenia, flushing, pain; *cardiovascular*: palpitations; *central nervous system*: insomnia, nervousness, paresthesia, somnolence; *dermatologic*: pruritus, rash; *gastrointestinal*: abdominal pain, diarrhea, dry mouth, dyspepsia, flatulence; *musculoskeletal*: arthralgia, leg cramps; *respiratory*: chest pain (nonspecific), dyspnea; *urogenital*: impotence, polyuria.

Other adverse reactions were reported sporadically with an incidence of 1.0% or less. These include: *body as a whole/systemic*: face edema, fever, hot flashes, malaise, periorbital edema, rigors; *cardiovascular*: arrhythmia, hypotension, increased angina, tachycardia, syncope; *central nervous system*: anxiety, ataxia, decreased libido, depression, hypertonia, hypoesthesia, migraine, paroniria, tremor, vertigo; *dermatologic*: alopecia, increased sweating, urticaria, purpura; *gastrointestinal*: eructation, gastroesophageal reflux, gum hyperplasia, melena, vomiting, weight increase; *musculoskeletal*: back pain, gout, myalgias; *respiratory*: coughing, epistaxis, upper respiratory tract infection, respiratory disorder, sinusitis; *special senses*: abnormal lacrimation, abnormal vision, taste perversion, tinnitus; *urogenital/reproductive*: breast pain, dysuria, hematuria, nocturia.

Adverse experiences which occurred in less than 1 in 1000 patients cannot be distinguished from concurrent disease states or medications.

The following adverse experiences, reported in less than 1% of patients, occurred under conditions (e.g., open trials, marketing experience) where a causal relationship is uncertain: gastrointestinal irritation, gastrointestinal bleeding.

In multiple-dose U.S. and foreign controlled studies with nifedipine capsules in which adverse reactions were reported spontaneously, adverse effects were frequent but generally not serious and rarely required discontinuation of therapy or dosage adjustment. Most were expected consequences of the vasodilator effects of Procardia. Adverse experiences reported in placebo-controlled trials include: dizziness, lightheadedness, and giddiness (27%, compared to 15% placebo incidence); flushing, heat sensation (25%, compared to 8% placebo incidence); headache (23%, compared to 20% placebo incidence); weakness (12%, compared to 10% placebo incidence); nausea, heartburn (11%, compared to 8% placebo incidence); muscle cramps, tremor (8%, compared to 3% placebo incidence); peripheral edema (7%, compared to 1% placebo incidence); nervousness, mood changes (7%, compared to 4% placebo incidence); palpitation (7%, compared to 5% placebo incidence); dyspnea, cough, and wheezing (6%, compared to 3% placebo incidence); and nasal congestion, sore throat (6%, compared to 8% placebo incidence).

There is also a large uncontrolled experience in over 2100 patients in the United States. Most of the patients had vasospastic or resistant angina pectoris, and about half had concomitant treatment with beta-adrenergic blocking agents. The relatively common adverse events were similar in nature to those seen with PROCARDIA XL.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

In a subgroup of over 1000 patients receiving Procardia with concomitant beta blocker therapy, the pattern and incidence of adverse experiences was not different from that of the entire group of Procardia treated patients (See PRECAUTIONS.)

In a subgroup of approximately 250 patients with a diagnosis of congestive heart failure as well as angina, dizziness or lightheadedness, peripheral edema, headache or flushing each occurred in one in eight patients. Hypotension occurred in about one in 20 patients. Syncope occurred in approximately one patient in 250. Myocardial infarction or symptoms of congestive heart failure each occurred in about one patient in 15. Atrial or ventricular dysrhythmias each occurred in about one patient in 150.

In post-marketing experience, there have been rare reports of exfoliative dermatitis caused by nifedipine.

More detailed professional information available on request.

Revised July 1990

Pfizer Labs

Sunday, November 11, 1990
Dallas, Texas

HEART FAILURE BEYOND ACE INHIBITION

This important symposium will present state-of-the-art information on treating congestive heart failure and the promise of future therapies

Place: Hotel Crescent Court
Crescent Ballroom
400 Crescent Court

Time: 8:30 am - 12:00 noon

A complimentary continental breakfast and luncheon will be served

Chairman:
Milton Packer, MD
New York, New York

Program:
State of the Art: Present Challenges
Jay N. Cohn, MD
Minneapolis, Minnesota

Mechanism of Action of New Vasodilators and Inotropes: Strategy for New Drug Development
Wilson S. Colucci, MD
Boston, Massachusetts

Limitations of Currently Available Vasodilators
Uri Elkayam, MD
Los Angeles, California

Limitations of Currently Available Positive and Negative Inotropic Agents
Barry M. Massie, MD
San Francisco, California

Vasodilator Therapy in the 90s: Promises and Predictions
Milton Packer, MD

Inotropic Therapy in the 90s: Promises and Predictions
Michael R. Bristow, MD, PhD
Salt Lake City, Utah

Discussion:
Treatment of Heart Failure in 1995
Milton Packer—Moderator

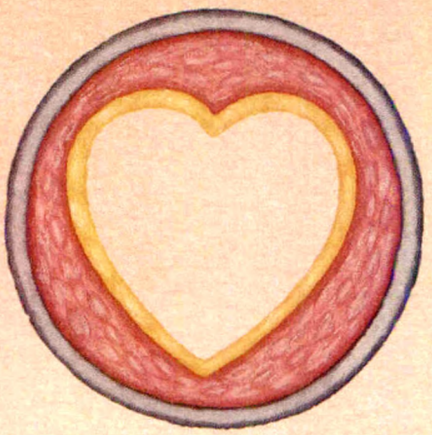
To register for this important symposium, please call Ms. Maureen Mulcahy toll-free at 800-527-7769; in New York State call 212-614-1359.

The Page and William Black Post-Graduate School of Medicine of the Mount Sinai School of Medicine (CUNY) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians and designates this Continuing Medical Education activity for 3 credit hours in Category 1 of the Physician's Recognition Award of the American Medical Association.

This program is supported by an educational grant from Boots Pharmaceuticals, Inc.

Look for your invitation in the mail.

Kindhearted



LOZOL® (indapamide)

No significant increases in cholesterol in most patients*

In long-term clinical trials, Lozol has demonstrated little or no effect on serum cholesterol levels.[1-3]

Minimal impact on potassium†

95% of patients showed no clinical hypokalemia in a long-term trial.[2]

ONE A DAY
LOZOL®
INDAPAMIDE 2.5mg

The diuretic that doesn't compromise cholesterol

*Lozol is not a cholesterol-lowering agent, nor has it been shown to reduce existing atherosclerotic plaque.
†Because of the diuretic effects of Lozol, changes in certain electrolytes can occur. Determination of serum electrolytes should therefore be performed.

LOZOL® (indapamide) **2.5 mg tablets**
BRIEF SUMMARY
INDICATIONS AND USAGE: Lozol® (indapamide) is indicated for the treatment of hypertension, alone or in combination with other antihypertensive drugs, and for the treatment of salt and fluid retention associated with congestive heart failure.
Usage in Pregnancy: See PRECAUTIONS.
CONTRAINDICATIONS: Anuria, hypersensitivity to indapamide or other sulfonamide-derived drugs.
WARNINGS: Hypokalemia occurs commonly with diuretics, and electrolyte monitoring is essential. In general, diuretics should not be given with lithium.
PRECAUTIONS: Perform serum electrolyte determinations at appropriate intervals, especially in patients who are vomiting excessively or receiving parenteral fluids, in patients subject to electrolyte imbalance, or in patients on a salt-restricted diet. In addition, patients should be observed for clinical signs of fluid or electrolyte imbalance, such as hyponatremia, hypochloremic alkalosis, or hypokalemia. The risk of hypokalemia secondary to diuresis and natriuresis is increased with larger doses, with brisk diuresis, with severe cirrhosis, and with concomitant use of corticosteroids or ACTH. Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis, such as increased ventricular irritability. Dilutional hyponatremia may occur in edematous patients; appropriate treatment is usually water restriction. In actual salt depletion, appropriate replacement is the treatment of choice. Chloride deficit is usually mild, not requiring specific treatment except in extraordinary circumstances (liver, renal disease).
Hyperuricemia may occur, and frank gout may be precipitated in certain patients receiving indapamide. Serum concentrations of uric acid should be monitored periodically.
Use with caution in patients with severe renal disease; consider withholding or discontinuing if progressive renal impairment is observed. Renal function tests should be performed periodically.
Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Latent diabetes may become manifest and insulin requirements in diabetic patients may be altered during thiazide administration. Serum concentrations of glucose should be monitored routinely during treatment with indapamide.
Calcium excretion is decreased by diuretics pharmacologically related to indapamide. Serum concentrations of calcium increased only slightly with indapamide in long-term studies of hypertensive patients. Indapamide may decrease serum PBI levels without signs of thyroid disturbance. Complications of hyperparathyroidism have not been seen. Discontinue before tests of parathyroid function are performed. Thiazides have exacerbated or activated systemic lupus erythematosus. Consider this possibility with indapamide.
DRUG INTERACTIONS: LOZOL may add to or potentiate the action of other antihypertensive drugs. The antihypertensive effect of the drug may be enhanced in the postsympathectomized patient. Indapamide may decrease arterial responsiveness to norepinephrine, but this does not preclude the use of norepinephrine.
In mouse and rat life-time carcinogenicity studies, there were no significant differences in the incidence of tumors between the indapamide-treated animals and the control groups.
Pregnancy Category B: Diuretics cross the placental barrier and appear in cord blood. Indapamide should be used during pregnancy only if clearly needed. Use may be associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse effects that have occurred in adults. It is not known whether this drug is excreted in human milk. If use of this drug is deemed essential, the patient should stop nursing.
ADVERSE REACTIONS: Most adverse effects have been mild and transient. From Phase II placebo-controlled studies and long-term controlled clinical studies, adverse reactions with $\geq$ 5% cumulative incidence: headache, dizziness, fatigue, weakness, loss of energy, lethargy, tiredness or malaise, muscle cramps or spasm, or numbness of the extremities, nervousness, tension, anxiety, irritability, or agitation; $<$ 5% cumulative incidence: lightheadedness, drowsiness vertigo, insomnia, depression, blurred vision, constipation, nausea, vomiting, diarrhea, gastric irritation, abdominal pain or cramps, anorexia, orthostatic hypotension, premature ventricular contractions, irregular heart beat, palpitations, frequency of urination, nocturia, polyuria, rash, hives, pruritus, vasculitis, impotence or reduced libido, rhinorrhea, flushing, hyperuricemia, hyperglycemia, hyponatremia, hypochloremia, increase in serum BUN or creatinine, glycosuria, weight loss, dry mouth, tingling of extremities. Clinical hypokalemia occurred in 3% and 7% of patients given indapamide 2.5 mg and 5.0 mg, respectively. In a long-term study (157 patients) potassium supplementation was given to 12% and 27% of patients on indapamide 2.5 mg and 5.0 mg, respectively.
Other adverse reactions reported with antihypertensive/diuretics are intrahepatic cholestatic jaundice, sialadenitis, xanthopsia, photosensitivity, purpura, necrotizing angiitis, fever, respiratory distress (including pneumonitis), anaphylactic reactions, agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia.
CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.
Keep tightly closed. Store at room temperature. Avoid excessive heat. Dispense in tight containers as defined in USP.
See product circular for full prescribing information. Revised: June 1990

References: 1. Meyer-Sabellek W, Gotzen R, Heitz J, et al: Serum lipoprotein levels during long-term treatment of hypertension with indapamide. *Hypertension* 1985;7(suppl 2): 170-174. **2.** Beling S, Vukovich RA, Neiss ES, et al: Long-term experience with indapamide. *Am Heart J* 1983; 106:258-262. **3.** Scalabrino A, Galeone F, Giuntoli F, et al: Clinical investigation on long-term effects of indapamide in patients with essential hypertension. *Curr Ther Res* 1984;35:17-22.

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CORONARY ARTERY DISEASE

The American Journal of Cardiology

NOVEMBER 1, 1990, VOL. 66, NO. 15

Percutaneous Excimer Laser Coronary Angioplasty

Frank Litvack, MD, Neal L. Eigler, MD, James R. Margolis, MD, Warren S. Grundfest, MD, Donald Rothbaum, MD, Thomas Linnemeier, MD, Lisa B. Hestrin, MPH, Daniel Tsoi, MD, Stephen L. Cook, MD, Daniel Krauthamer, MD, Tsvi Goldenberg, PhD, James R. Laudenslager, PhD, Jacob Segalowitz, MD, and James S. Forrester, MD

To determine the efficacy of percutaneous excimer laser coronary angioplasty as an adjunct or alternative to conventional balloon angioplasty, 55 patients were studied in a multicenter trial. These patients underwent the procedure using a modification of conventional balloon angioplasty technique. A first-generation, 1.6-mm diameter catheter constructed of 12 individual silica fibers concentrically arranged around a guidewire lumen was used. Catheter tip energy density varied from 35 to 50 mJ/mm^2. The mean number of pulses delivered at 20 Hz was 1,272 ± 1,345. Acute success was defined as a ≥20% increase in stenotic diameter and a lumen of ≥1 mm in diameter after laser treatment. Acute success was achieved in 46 of 55 (84%) patients. Adjunctive balloon angioplasty was performed on 41 patients (75%). The percent diameter stenosis as determined by quantitative angiography decreased from a baseline of 83 ± 14 to 49 ± 11% after laser treatment and to 38 ± 12% in patients undergoing adjunctive balloon angioplasty. The mean minimal stenotic diameter increased from a baseline of 0.5 ± 0.4 to 1.6 ± 0.5 mm after laser treatment and to 2.1 ± 0.5 mm after balloon angioplasty. There were no deaths and no vascular perforations. One patient (1.8%) required emergency coronary bypass surgery. These data suggest that excimer laser energy delivered percutaneously by specially constructed catheters can safely ablate atheroma and reduce coronary stenoses.

(Am J Cardiol 1990;66:1027–1032)

From the Department of Medicine, Division of Cardiology, Cedars-Sinai Medical Center and the University of California at Los Angeles School of Medicine, Los Angeles, California; South Miami Hospital, Miami, Florida; St. Vincent's Hospital, Indianapolis, Indiana; and Advanced Interventional Systems, Inc., Irvine, California. This grant was supported in part by National Institutes of Health SCOR Grant HL-17651. Manuscript received May 9, 1990; revised manuscript received and accepted June 14, 1990.

Address for reprints: Frank Litvack, MD, Cedars-Sinai Medical Center, Room 6537, Los Angeles, California 90048.

In the last decade the number of percutaneous transluminal coronary angioplasties (PTCA) increased from 10,000 to 250,000 cases per year and is projected to reach 450,000 by 1993.[1] Despite the documented efficacy of PTCA,[2] an important fundamental limitation is that balloon inflation does not reduce atheroma mass. Recent angioscopy and autopsy studies show fissures in the atheroma after PTCA,[3] and it is now postulated that a major component of the angiographic appearance of improved vascular diameter results from stretching the normal vascular wall in the eccentric coronary lesion.[4] Consequently, there is an ongoing search for intravascular interventions that might reduce the mass of the atheroma by drilling, extraction, or ablation with various forms of laser energy.[5,6]

In contrast to thermal lasers, the pulsed excimer laser has been shown to ablate even calcified tissue with minimal thermal injury.[7,8] In the past year, using a single fiber system, we reported a recanalization rate (77%) in peripheral vascular occlusions similar to that previously reported for thermal lasers.[9] We found, however, that vascular perforation could occur when the laser delivery catheter came into contact with the lateral vessel wall. We designed a multiple fiberoptic bundle that could be passed over a conventional coronary angioplasty guidewire. This allowed us to maintain the flexible catheter tip coaxial to the long axis of the vessel, even in moving tortuous coronary arteries. In August 1988 we performed the first successful percutaneous coronary excimer laser angioplasty in humans.[10] We have also reported the successful recanalization of aortocoronary saphenous vein grafts by excimer laser energy.[11] This article details our initial, acute experience in an ongoing prospective, nonrandomized, multicenter clinical trial of coronary excimer laser angioplasty.

METHODS

Criteria for patient entry: This report covers the first 55 patients in whom excimer laser coronary angioplasty was attempted at 3 institutions. The first procedure was performed in August 1988. The trial began at Cedars-Sinai Medical Center, Los Angeles, California, then expanded to South Miami Hospital, Miami, Florida, in March 1989 and to St. Vincent's Hospital, Indianapolis,

Indiana, in May 1989. Permission had been granted by the United States Food and Drug Administration and each institution received approval from its internal review board.

Patients were considered for this trial if they had (1) coronary artery disease with symptoms, ischemia sufficient to warrant balloon angioplasty or bypass surgery, or both; (2) angiographically documented obstructive disease in native coronary arteries or vein grafts; and (3) a coronary artery stenosis or occlusion thought to be traversable with a guidewire. Patients were excluded if they had a nonbypassed left main stenosis >50% in diameter, a coexisting terminal medical illness or were unable to give informed consent.

Patient population: Of the 55 patients, 25 had the procedure performed at Cedars-Sinai Medical Center, 25 at South Miami Hospital and 5 at St. Vincent's Hospital. Twenty-nine patients (53%) had anginal symptoms classified as Canadian Cardiovascular Society functional classification III or IV, and 19 patients (35%) had ≥1 prior balloon angioplasties of the treated lesion. There were 67 narrowings treated, of which 56 (84%) were in native coronary arteries and 6 (9%) were in bypass grafts; 11 (16%) were total occlusions and 56 (84%) were stenoses.

Method of data collection: All clinical, laboratory and angiographic data were collected on computer-ready data forms at the individual treatment locations and were forwarded to the Data Coordinating Center at Cedars-Sinai. In addition, every pre- and post-procedure coronary angiogram was sent to Cedars-Sinai for quantitative coronary angiographic analysis by the Angiography Coordinating Center. The data form is compatible with the National Heart, Lung, and Blood Institute PTCA Data Registry.[12] The same definitions for angina severity and for coronary angiographic classification were used. In addition to obtaining clinical and angiographic patient profiles, we recorded 12-lead electrocardiograms and serum creatine kinase levels on the evening of and the morning immediately after the procedure in each patient. Our ongoing follow-up protocol includes evaluation of clinical status before hospital discharge at 1 and 6 months, at which time all patients are to have thallium-201 treadmill exercise tests and will be asked to undergo repeat coronary angiography.

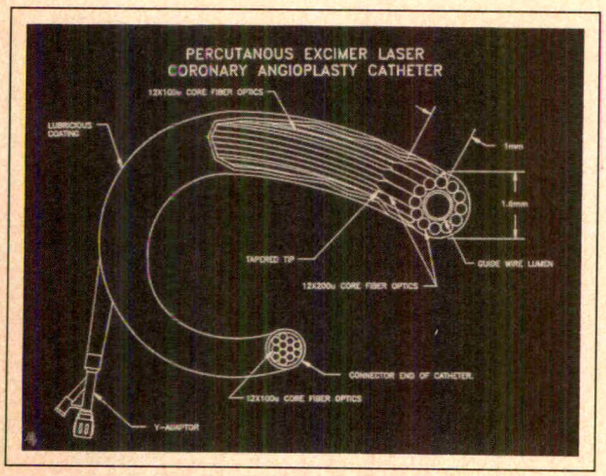


FIGURE 1. Schematic of 1.6-mm diameter excimer laser coronary catheter. Twelve individual, 100-μ silica fibers with 200-μ tips are concentrically arranged around the lumen for up to an 0.018-inch coronary guidewire. Lesions are first crossed with a guidewire and excimer angioplasty is performed at 35 to 50 mJ/mm² by direct contact of the catheter tip with the atheroma.

Excimer laser source: We used a magnetically switched, thyratron-driven 308-nm xenon chloride excimer laser specifically designed for intravascular use (Advanced Interventional Systems, Inc., Irvine, California). The laser emits up to 225 mJ/pulse at 5 to 50 Hz and has a 180-ns pulse duration. The laser uses single phase 208 volt current. A detailed description of the electronic specifications of this device has been published.[13]

Fiberoptic catheter delivery system: The fiberoptic delivery catheter, which we designed for coronary use, has a 4.7Fr (1.6-mm diameter) flexible polyethylene shaft with a proximal Y adapter for insertion of a coronary guidewire and for connection of the fiberoptics to the laser power source. The catheter has a central lumen that accepts a 0.018-inch diameter standard coronary guidewire. In concentric array around this lumen are 12 individual, substantially pure 100-μ shaft silica fibers with 200-μ tips (Figure 1). The tips are flush with the distal tip of the catheter.

Excimer laser coronary angioplasty procedure: All prior medications were continued. Aspirin, 80 mg twice each day, and a calcium channel antagonist were given no later than the day before the procedure if not already prescribed. All 55 procedures were performed using standard percutaneous femoral artery technique and conventional 8Fr angioplasty guide catheters. Our protocol called for baseline cineangiography in ≥2 projections that best demonstrated the lesions separated by ≥60°. The position of the x-ray tubes and image intensifiers was recorded and completion views in the same projections were obtained. Heparin 10,000 to 15,000 IU was administered intravenously.

The laser procedure was performed by crossing the lesion with a conventional 0.018-inch guidewire (Advanced Cardiovascular Systems, Inc., San Jose, California) under fluoroscopic control. The laser catheter was then advanced over the guidewire and positioned with its tip in contact with the proximal margin of the lesion. Excimer angioplasty was then performed under fluoroscopic guidance. Energy emitted from the catheter tip was set at 35 to 50 mJ/mm² per pulse at 20 Hz. The operator advanced the catheter slowly, at not more than 1 to 3 mm/s during laser emission, until the lesion was crossed. Each time that the catheter passed completely across the lesion, the catheter was withdrawn and angiographic injection performed. Multiple (2 to 5) passes through the lesion were made to enlarge the lumen. The laser catheter was then withdrawn with the guidewire left across the lesion, and cineangiography was performed in ≥1 view. If the stenosis after treatment was visually estimated to be <50% diameter, then completion angiograms were recorded in 2 views. If the residu-

al stenosis was >50%, then balloon angioplasty was performed before completion angiography. Catheters were withdrawn and the arterial introducer sheaths sutured into place. All patients continued to be maintained on their medications and on a heparin infusion (600 to 1,200 IU/hour) until the next day, when the heparin was discontinued and the sheaths removed. Subsequent treatment followed routine postangioplasty standards.

Quantitative coronary angiography: All angiograms were acquired on 35-mm cinefilm at 30 to 45 frames/s using 5- to 7-inch image intensifier field sizes. Quantitative coronary angiography was performed on all patients at baseline, after excimer laser angioplasty, and after balloon angioplasty on the projection that most clearly demonstrated the smallest minimal diameter stenosis, using the method described by Brown et al.[14] The reviewer was a cardiologist who neither performed the procedure nor had knowledge of the clinical results.

Cineangiograms were magnified 5 times (Vangard Instruments, Inc., Melville, New York) and viewed on a 26-inch rear projected digitizing screen (LW International, Inc., Woodland Hills, California). The operator traced the edges of the guiding catheter by hand with a crosshair cursor to calibrate magnification for each coronary injection. The luminal borders of the stenotic region were traced from a proximal to a distal identifiable branch point on 3 successive diastolic frames. No correction for pincushion distortion was made (these errors are typically <2%). The computer calculated the centerline of the vessel then computed its perpendicular diameter at 0.1-mm intervals. The edges were smoothed by a 7-point unweighted average. The parameters calculated were the minimum and maximum diameters, and the percent diameter stenosis. Only the most severe stenosis in each vessel was quantified. The mean intra- and interobserver variability for minimal stenotic diameter in our laboratory is <0.15 mm.

For classification, total occlusion was defined as no anterograde flow; subtotal stenosis was defined as no visible column of contrast across the stenosis with visible anterograde flow. For quantitative analysis, total occlusion was defined as a minimum stenotic diameter of 0.0

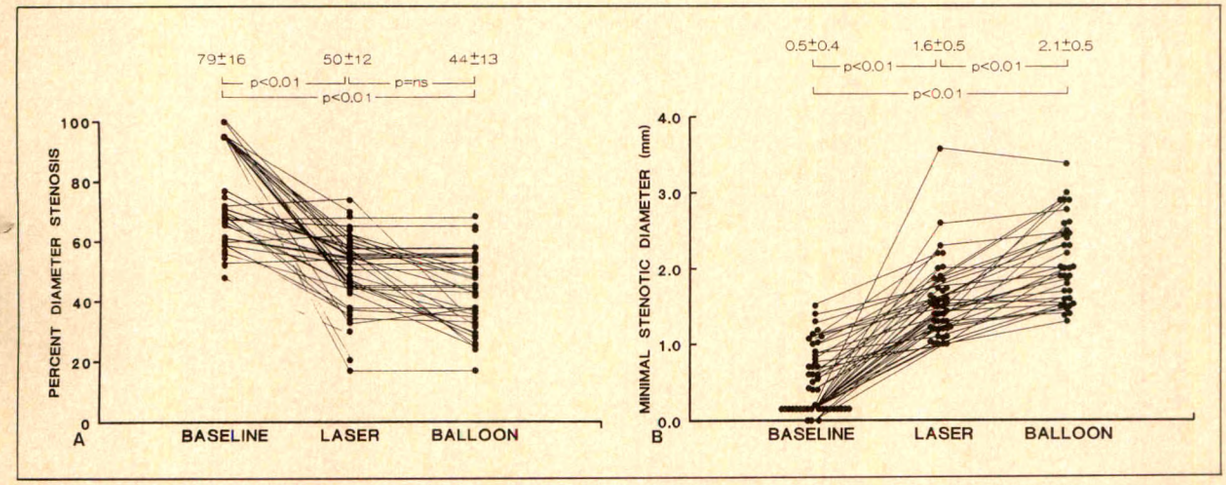


FIGURE 2. ***A*, mean baseline percent diameter stenosis of 83 ± 14%, which was reduced to 49 ± 11% (p <0.01) by laser and to 38 ± 12% (p <0.01) by balloon.** ***B*, the minimal stenotic diameter increased from a baseline of 0.5 ± 0.4 to 1.6 ± 0.5 mm after laser treatment (p <0.01) and to 2.1 ± 0.5 mm after balloon angioplasty (p <0.01).**

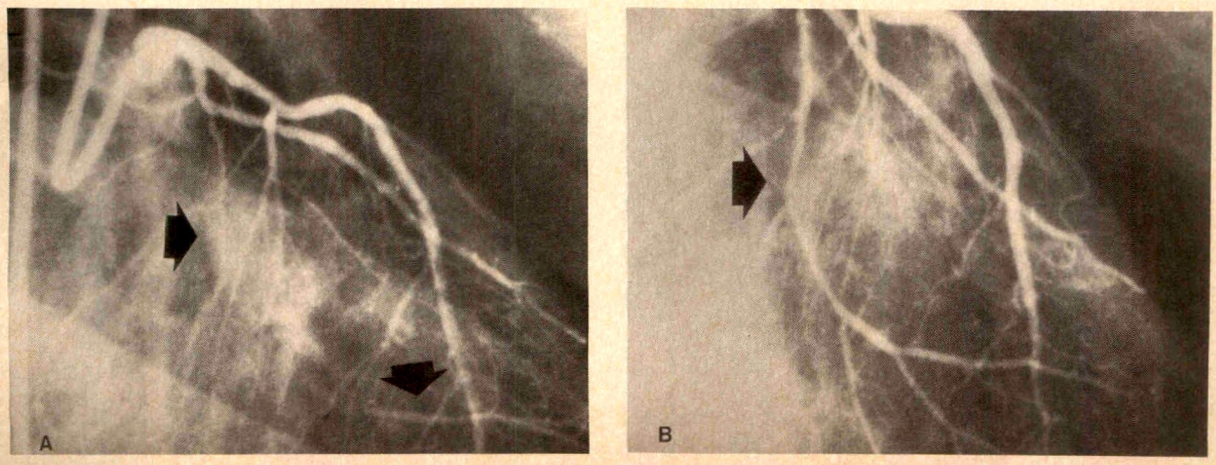


FIGURE 3. ***A*, a diffusely diseased left circumflex artery in a 54-year-old man with a long (4 cm) subtotal stenosis (*horizontal arrow*). The distal portion of the obtuse marginal branch is filled in part by left-to-left collateral vessels (*vertical arrow*).** ***B*, a recanalized 1.4-mm lumen (*arrow*) after excimer laser angioplasty alone with 2,400 pulses at 45 mJ/mm^2.**

mm; subtotal stenoses were assigned a value of 0.15 mm (half the width of the image intensifier point spread function).

Definition used in data analysis: Laser angioplasty was classifed as successful if there was a >20% improvement in the absolute minimal stenotic diameter and if the vessel diameter was >1.0 mm. Myocardial infarction after the procedure was defined as creatine kinase elevation >20 CK-MB units; if creatine kinase levels rose without electrocardiographic Q waves, it was defined as a non-Q-wave infarction.

Statistical analysis: Student's *t* test was performed for pairwise comparisons. In the case of ≥3 samples, significance was tested by the 1-way analysis of variance. Multiple comparisons were performed using the Bonferoni modification of the t statistic.

RESULTS

Laser angioplasty was performed on 67 lesions in 56 arteries. The excimer procedure required a mean of 1,272 ± 1,345 (range 0 to 6,760) pulses; thus, at 20 Hz the mean laser operating time was 64 seconds. The 2 patients who had no pulses delivered had a laser catheter inserted into the coronary artery, but the lesions could not be reached. Acute success was achieved in 46 of 55 (84%) patients and in 56 of 67 (84%) sites. The 9 failures were due to failure to cross the lesion with the guidewire (1 patient); failure to reach the lesion with the laser catheter (n = 2); arterial dissection and closure (n = 1); inability to recanalize the entire lesion sufficiently (n = 4); and failure of the fiberoptic bundle to transmit light because of fracture at the Y adapter (n = 1). Of these 9 patients, 5 had successful completion of balloon angioplasty (final stenosis <50%) for a combined procedure success rate of 51 of 55 (92.7%). Of the patients treated successfully with the laser, 10 (22%) had laser treatment alone and 36 (78%) also had completion of balloon angioplasty. The mean diameter of the inflated balloon used was 2.7 ± 0.5 mm (range 2.0 to 4.0).

Figure 2A shows the quantitative angiography results. The mean diameter stenosis of 83 ± 14% before the procedure was significantly reduced to 49 ± 11% ($p < 0.01$) by laser and was further reduced to 38 ± 12% ($p < 0.01$) in the patients who also had completion of balloon angioplasty. Figure 2B shows that the minimal

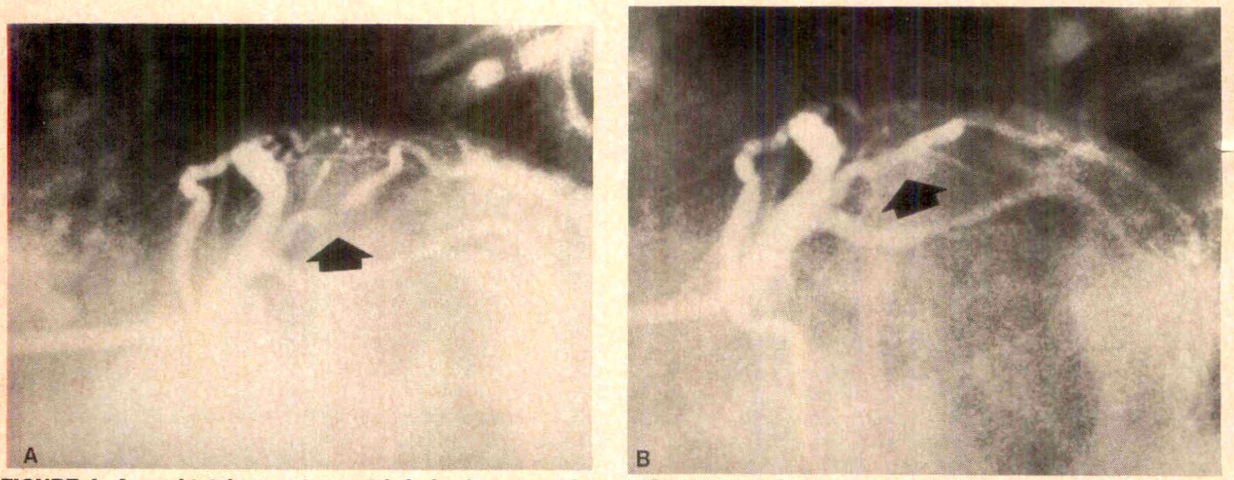


FIGURE 4. *A*, a subtotal percent eccentric lesion in a ramus intermediate artery. *B*, after excimer angioplasty with 871 pulses at a 42 mJ/mm², a residual stenosis of 23% remains.

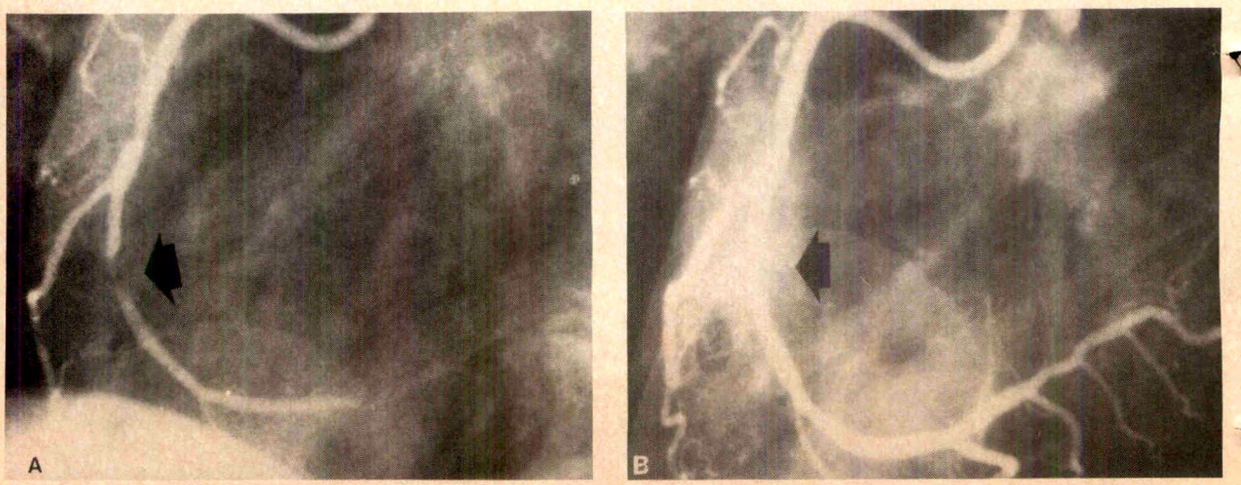


FIGURE 5. *A*, a focal subtotal stenosis in the midright coronary artery. *B*, after excimer angioplasty with 292 pulses at 40 mJ/mm², there is a residual 29% stenosis.

stenotic diameter improved from 0.5 ± 0.4 to 1.6 ± 0.5 mm ($p < 0.01$) after laser and further increased to 2.1 ± 0.5 ($p < 0.01$) in the patients who underwent balloon angioplasty. There was no significant difference between lumen diameter after laser in patients who had laser treatment alone and lumen diameter in patients who also had completion of balloon angioplasty (1.7 ± 0.4 vs 1.6 ± 0.5 mm). The laser-only group had a lower percent stenosis after treatment (40 ± 11 vs 51 ± 10%) because the normal arterial segments were generally smaller in this group.

Figures 3 through 5 show case examples. Figure 3 shows the use of the excimer laser in diffuse coronary disease. Figure 3A shows the left circumflex artery of a 54-year-old man with a long (4 cm) subtotal stenosis. Figure 3B shows the recanalized channel after excimer angioplasty alone. The minimum stenotic diameter is 1.4 mm, with anterograde filling of the distal artery.

Figure 4A shows the use of the excimer laser in an eccentric lesion. Before laser, there is a 95% eccentric stenosis in a large ramus intermediate artery of a 65-year-old man. After excimer angioplasty, the residual stenosis is 23% with a 1.6-mm minimum diameter.

Figure 5 shows stand-alone excimer laser angioplasty in a focal, subtotal stenosis of the midright coronary artery in a 48-year-old man. After excimer angioplasty there is a residual 29% stenosis and the minimum stenotic diameter is 1.9 mm.

Complications: There were no deaths or vascular perforations. Clinically significant complications occurred in 3 patients (5%). Emergency coronary bypass surgery was required in 1 patient who 3 weeks prior had a failed PTCA with a left anterior descending coronary artery dissection. The laser procedure worsened rather than improved the dissection, and led to acute closure and emergency coronary bypass surgery, from which the patient recovered uneventfully. One patient developed transient occlusion of the left anterior descending artery, thought to be secondary to vasospasm. The artery was reopened using balloon dilatation and intracoronary vasodilators. A non-Q-wave myocardial infarction subsequently evolved and the patient had an uneventful postoperative course. Another patient, who developed a linear angiographic dissection after laser ablation of a 2-cm-long eccentric lesion of the left circumflex artery, had completion of balloon angioplasty, an adequate final angiographic result, an uneventful hospital course, and was discharged on day 2. On day 3 this patient complained of sudden onset of chest pain. Angiography revealed that the artery was totally occluded but was filling through right-to-left collateral vessels. No enzymatic or electrocardiographic evidence of myocardial infarction developed and the patient was classified as an early closure without infarction. In addition, 2 patients developed transient vasospasm and 2 others developed uncomplicated angiographic dissection without sequelae.

DISCUSSION

We report an acute success rate of 84% in the first 55 patients whom we treated with percutaneous excimer laser coronary angioplasty. The complication rate (infarction, emergency surgery, dissection) was comparable to that reported for balloon angioplasty performed in experienced medical centers,[12] and there were no cases of vascular perforation or death. Thus, our study demonstrates the feasibility of excimer laser angioplasty as an alternative treatment for patients with coronary artery disease. The potential import of our results is that the laser can remove atheromatous obstructions rather than stretching the normal wall, displacing the atheroma, or bypassing it.

Our study also revealed the limitations of this first-generation technology. Although 14 patients had stand-alone excimer angioplasty, 31 patients required adjunctive balloon angioplasty for an angiographically acceptable final result. This limitation was because we used a 1.6-mm diameter catheter for ablation. Our results show that the mean minimum arterial diameter after angioplasty with a 1.6-mm diameter catheter is 1.6 mm. Thus, large diameter (>3.0 mm) coronary arteries and vein grafts had significant residual stenosis after laser angioplasty. Consequently, we have made design modifications to produce catheters of 2.0 and 2.4 mm in diameter, which have the potential to allow stand-alone excimer angioplasty in the majority of coronary artery segments.

Results of quantitative coronary angiography illustrate the difference between the excimer laser and balloon angioplasty as a mechanism for recanalization. The mean diameter lumen, 1.6 mm, after laser treatment corresponds to the outer diameter of the catheter. In contrast, the mean diameter lumen, 2.1 mm, after balloon angioplasty is less than the mean balloon diameter used in our study. These data are consistent with the widely held view that the laser operates by ablation and the balloon by fracture and stretching.[5,15]

The patient who required emergency bypass surgery had a preexisting arterial dissection caused by a failed balloon angioplasty. The laser procedure then caused an abrupt arterial closure. This was our fourth patient, and we now avoid using the excimer laser catheter in patients who have had dissections. Another patient developed intense, prolonged vasospasm of arterial segments distal to the excimer ablation sites, which resolved only after large doses of vasodilators, suggesting local release of either particulate material or vasoactive compounds. No other patient has had a similar response. The absence of the more serious complications of vascular perforation implies that the "over-the-wire" multifiber excimer catheter can be used in a variety of arterial contours without a high risk of perforation. We believe that this outcome derives from 3 properties of the system: the coaxial position of the catheter tip over the leading guidewire, the absence of significant tissue heating during excimer ablation,[5] and the absence of excimer energy transmission through blood,[8] so that the laser catheter ablates only on direct contact.

Our report deals only with acute recanalization. Our follow-up is ongoing and will require more patients for meaningful analysis. Specifically, patency data must be classified by lesion location (native vessels, grafts, ostial, and so forth), type of procedure (balloon adjunctive or laser stand-alone), stenosis morphology (length, calcifi-

cation, and so forth) and the number of prior procedures performed on the treated lesion. Consequently, meaningful determination of recurrence rates after excimer angioplasty must await the completion and analysis of angiographic follow-up studies on a larger number of patients. Comparison with balloon angioplasty may well require a randomized trial.

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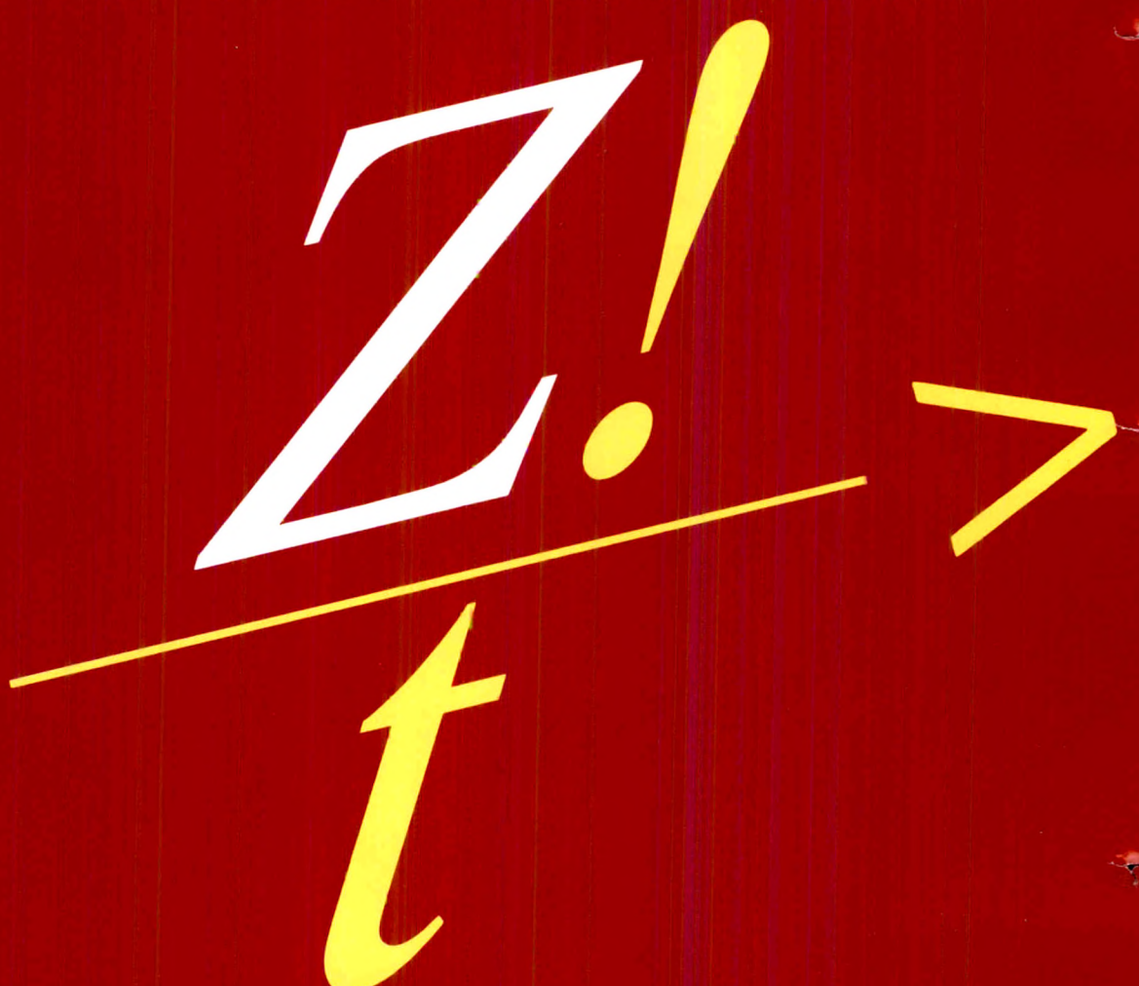
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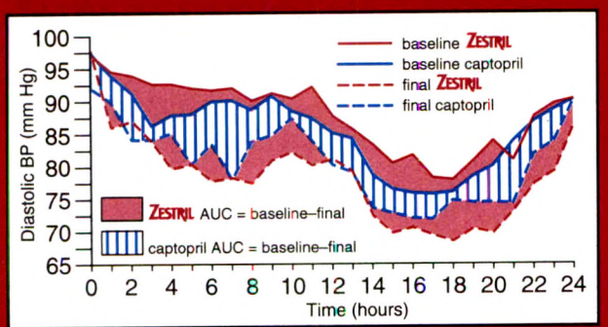
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INDICATIONS AND USAGE. ZESTRIL is indicated for the treatment of hypertension. It may be used alone as initial therapy or concomitantly with other classes of antihypertensive agents. In using ZESTRIL, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that ZESTRIL does not have a similar risk. (See WARNINGS.) **CONTRAINDICATIONS.** ZESTRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor. **WARNINGS. Angioedema:** Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including ZESTRIL. In such cases, ZESTRIL should be promptly discontinued, and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, eg, subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) should be promptly administered. (See ADVERSE REACTIONS.) Hypotension:** Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of use with ZESTRIL in salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of ZESTRIL and/or diuretic is increased. Similar considerations apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion. **Neutropenia/Agranulocytosis:** Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of ZESTRIL are insufficient to show that ZESTRIL does not cause agranulocytosis at similar rates. Marketing experience has revealed rare cases of neutropenia and bone marrow depression in which a causal relationship to lisinopril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered. **PRECAUTIONS. General. Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including ZESTRIL, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of ZESTRIL and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when ZESTRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of ZESTRIL and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.) Hyperkalemia:** In clinical trials hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 2.2% of hypertensive patients and 4.0% of patients with congestive heart failure. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in approximately 0.1% of hypertensive patients. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ZESTRIL. (See Drug Interactions.) **Surgery/Anesthesia:** In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ZESTRIL may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion. **Information for Patients. Angioedema:** Angioedema, including laryngeal edema, may occur especially following the first dose of ZESTRIL. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician. **Symptomatic Hypotension:** Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patient should be told to discontinue the drug until they have consulted with the prescribing physician. All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with their physician. **Hyperkalemia:** Patients should be told not to use salt substitutes containing potassium without consulting their physician. **Neutropenia:** Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which may be a sign of neutropenia. **NOTE:** As with many other drugs, certain advice to patients being treated with ZESTRIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. **DRUG INTERACTIONS. Hypotension – Patients on Diuretic Therapy:** Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ZESTRIL. The possibility of hypotensive effects with ZESTRIL can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with ZESTRIL. If it is necessary to continue the diuretic, initiate therapy with ZESTRIL at a dose of 5 mg daily, and provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS, and DOSAGE AND ADMINISTRATION.) When a diuretic is added to the therapy of a patient receiving ZESTRIL, an additional antihypertensive effect is usually observed. Studies with ACE inhibitors in combination with diuretics indicate that the dose of the ACE inhibitor can be reduced when it is given with a diuretic. (See DOSAGE AND ADMINISTRATION.) **Indomethacin:** In a study in 36 patients with mild to moderate hypertension where the antihypertensive effects of ZESTRIL alone were compared to ZESTRIL given concomitantly with indomethacin, the use of indomethacin was associated with a reduced effect, although the difference between the two regimens was not significant. **Other Agents:** ZESTRIL has been used concomitantly with nitrates and/or digoxin without evidence of clinically significant adverse interactions. No clinically important pharmacokinetic interactions occurred when ZESTRIL was used concomitantly with propranolol or hydrochlorothiazide. The presence of food in the stomach does not alter the bioavailability of ZESTRIL. **Agents Increasing Serum Potassium:** ZESTRIL attenuates potassium loss caused by thiazide-type diuretics. Use of ZESTRIL with potassium-sparing diuretics (eg, spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. **Lithium:** Lithium toxicity has been reported in patients receiving lithium with drugs which cause elimination of sodium, including ACE inhibitors. Lithium toxicity was usually reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if ZESTRIL is administered concomitantly with lithium. **Carcinogenesis, Mutagenesis, Impairment of Fertility.** There was no evidence of a tumorigenic effect when lisinopril was administered for 105 weeks to male and female rats at doses up to 90 mg/kg/day (about 56 times* the maximum recommended daily human dose) or when lisinopril was administered for 92 weeks to (male and female) mice at doses up to 135 mg/kg/day (about 84 times* the maximum recommended daily human dose). *Based on patient weight of 50 kg. Lisinopril was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. It was also negative in a forward mutation assay using Chinese hamster lung cells. Lisinopril did not produce single strand DNA breaks in an in vitro alkaline elution rat hepatocyte assay. In addition, lisinopril did not produce increases in chromosomal aberrations in an in vitro test in Chinese hamster ovary cells or in an in vivo study in mouse bone marrow. There were no adverse effects on reproductive performance in male and female rats treated with up to 300 mg/kg/day of lisinopril. **Pregnancy. Pregnancy Category C:** Lisinopril was not teratogenic in mice treated on days 6-15 of gestation with up to 1,000 mg/kg/day (625 times the maximum recommended human dose). There was an increase in fetal resorptions at doses down to 100 mg/kg; at doses of 1,000 mg/kg this was prevented by saline supplementation. There was no fetotoxicity or teratogenicity in rats treated with up to 300 mg/kg/day (188 times the maximum recommended dose) of lisinopril at days 6-17 of gestation. In rats receiving lisinopril from day 15 of gestation through day 21 postpartum, there was an increased incidence in pup deaths on days 2-7 postpartum and a lower average body weight of pups on day 21 postpartum. The increase in pup deaths and decrease in pup weight did not occur with maternal saline supplementation. Lisinopril, at doses up to 1 mg/kg/day, was not teratogenic when given throughout the organogenic period in saline supplemented rabbits. Saline supplementation (physiologic saline in place of tap water) was used to eliminate maternotoxic effects and enable evaluation of the teratogenic potential at the highest possible dosage level. The rabbit has been shown to be extremely sensitive to angiotensin converting enzyme inhibitors (captopril and enalapril) with maternal and fetotoxic effects apparent at or below the recommended therapeutic dosage levels in man. Fetotoxicity was demonstrated in rabbits by an increased incidence of fetal resorptions at an oral dose of lisinopril of 1 mg/kg/day and by an increased incidence of incomplete ossification at the lowest dose tested (0.1 mg/kg/day). A single intravenous dose of 15 mg/kg of lisinopril administered to pregnant rabbits on gestation days 16, 21 or 26 resulted in 88% to 100% fetal death. By whole body autoradiography, radioactivity was found in the placenta following administration of labeled lisinopril to pregnant rats, but none was found in the fetuses. **Human Experience:** There are no adequate and well-controlled studies of lisinopril in pregnant women. However, data are available that show drugs of this class cross the human placenta. Because the risk of fetal toxicity with the use the ACE inhibitors has not been clearly defined (see below), lisinopril should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Postmarketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy

ZESTRIL® (lisinopril)

outcome. Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely. Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality. When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Infants exposed in utero to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate. Problems associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypertension or the underlying prematurity. Another ACE inhibitor, enalapril, has been removed from the neonatal circulation by peritoneal dialysis and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure. There is no experience with either of these procedures for removing lisinopril or other ACE inhibitors from the neonatal circulation. **Nursing Mothers:** Milk of lactating rats contains radioactivity following administration of ^{14}C lisinopril. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caut on should be exercised when ZESTRIL is given to a nursing mother. **Pediatric Use:** Safety and effectiveness in children have not been established. **ADVERSE REACTIONS.** ZESTRIL has been found to be generally well tolerated in controlled clinical trials involving 2003 patients and subjects. The most frequent clinical adverse experiences in controlled trials with ZESTRIL were dizziness (6.3%), headache (5.3%), fatigue (3.3%), diarrhea (3.2%), upper respiratory symptoms (3.0%), and cough (2.9%), all of which were more frequent than in placebo-treated patients. For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0% of patients. In clinical trials, the overall frequency of adverse experiences could not be related to total daily dosage within the recommended therapeutic dosage range. For adverse experiences which occurred in more than 1% of patients and subjects treated with ZESTRIL or ZESTRIL plus hydrochlorothiazide in controlled clinical trials, comparative incidence data are listed in the table below.

Percent of Patients in Controlled Studies

	ZESTRIL (n = 2003†) Incidence (discontinuation)	ZESTRIL/Hydrochlorothiazide (n = 644) Incidence (discontinuation)	Placebo (n = 207) Incidence
Dizziness	6.3 (0.6)	9.0 (0.9)	1.9
Headache	5.3 (0.2)	4.3 (0.5)	1.9
Fatigue	3.3 (0.2)	3.9 (0.5)	1.0
Diarrhea	3.2 (0.3)	2.6 (0.3)	2.4
Upper Respiratory Symptoms	3.0 (0.0)	4.5 (0.0)	0.0
Cough	2.9 (0.4)	4.5 (0.8)	1.0
Nausea	2.3 (0.3)	2.5 (0.2)	2.4
Hypotension	1.8 (0.8)	1.6 (0.5)	0.5
Rash	1.5 (0.4)	1.6 (0.2)	0.5
Orthostatic Effects	1.4 (0.0)	3.4 (0.2)	1.0
Asthenia	1.3 (0.4)	2.0 (0.2)	1.0
Chest Pain	1.3 (0.1)	1.2 (0.2)	1.4
Vomiting	1.3 (0.2)	1.4 (0.0)	0.5
Dyspnea	1.1 (0.0)	0.5 (0.2)	1.4
Dyspepsia	1.0 (0.0)	1.9 (0.0)	0.0
Paresthesia	0.8 (0.0)	2.0 (0.2)	0.0
Impotence	0.7 (0.2)	1.6 (0.3)	0.0
Muscle Cramps	0.6 (0.0)	2.8 (0.6)	0.5
Back Pain	0.5 (0.0)	1.1 (0.0)	1.4
Nasal Congestion	0.3 (0.0)	1.2 (0.0)	0.0
Decreased Libido	0.2 (0.1)	1.2 (0.0)	0.0
Vertigo	0.1 (0.0)	1.1 (0.2)	0.0

†Includes 420 patients treated for congestive heart failure who were receiving concomitant digitalis and/or diuretic therapy.

Clinical adverse experiences occurring in 0.3% to 1.0% of patients in the controlled trials and rarer, serious, possibly drug related events reported in uncontrolled studies or marketing experience are listed below and, within each category, are in order of decreasing severity. BODY AS A WHOLE: Chest discomfort, fever, flushing, malaise. CARDIOVASCULAR: Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, Hypotension); angina pectoris, orthostatic hypotension, rhythm disturbances, tachycardia, peripheral edema, vasculitis, palpitation. DIGESTIVE: Pancreatitis, abdominal pain, anorexia, constipation, flatulence, dry mouth. METABOLISM: Gout. MUSCULOSKELETAL: Joint pain, shoulder pain. NERVOUS SYSTEM/PSYCHIATRIC: Depression, somnolence, insomnia, stroke, nervousness, confusion. RESPIRATORY SYSTEM: Bronchitis, sinusitis, pharyngeal pain. SKIN: Urticaria, pruritus, diaphoresis. SPECIAL SENSES: Blurred vision. UROGENITAL: Oliguria, progressive azotemia, acute renal failure, urinary tract infection. A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia and fever. ANGIOEDEMA: Angioedema has been reported in patients receiving ZESTRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with ZESTRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.) HYPOTENSION: In hypertensive patients, hypotension occurred in 1.2% and syncope occurred in 0.1% of patients. Hypotension or syncope was a cause of discontinuation of therapy in 0.5% of hypertensive patients. (See WARNINGS.) In patients with congestive heart failure, hypotension occurred in 5.0% and syncope occurred in 1.0% of patients. These adverse experiences were causes for discontinuation of therapy in 1.3% of these patients. **Clinical Laboratory Test Findings. Serum Electrolytes:** Hyperkalemia. (See PRECAUTIONS.) **Creatinine, Blood Urea Nitrogen:** Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 2.0% of patients with essential hypertension treated with ZESTRIL alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis. (See PRECAUTIONS.) Reversible minor increases in blood urea nitrogen and serum creatinine were observed in approximately 9.1% of patients with congestive heart failure on concomitant diuretic therapy. Frequently, these abnormalities resolved when the dosage of the diuretic was decreased. **Hemoglobin and Hematocrit:** Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.4 g% and 1.3 vol%, respectively) occurred frequently in patients treated with ZESTRIL but were rarely of clinical importance in patients without some other cause of anemia. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia. **Other (Causal Relationship Unknown):** Rarely, elevations of liver enzymes and/or serum bilirubin have occurred. In marketing experience, rare cases of neutropenia and bone marrow depression have been reported. Overall, 2.0% of patients discontinued therapy due to laboratory adverse experiences, principally elevations in blood urea nitrogen (0.6%), serum creatinine (0.5%), and serum potassium (0.4%). **DOSAGE AND ADMINISTRATION. Initial Therapy:** In patients with uncomplicated essential hypertension not on diuretic therapy, the recommended initial dose is 10 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 20-40 mg per day administered in a single daily dose. The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with a dose of 10 mg daily. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, an increase in dose should be considered. Doses up to 80 mg have been used but do not appear to give greater effect. If blood pressure is not controlled with ZESTRIL alone, a low dose of a diuretic may be added. Hydrochlorothiazide, 12.5 mg has been shown to provide an additive effect. After the addition of a diuretic, it may be possible to reduce the dose of ZESTRIL. **Diuretic Treated Patients:** In hypertensive patients who are currently being treated with a diuretic, symptomatic hypotension may occur occasionally following the initial dose of ZESTRIL. The diuretic should be discontinued, if possible, for two to three days before beginning therapy with ZESTRIL to reduce the likelihood of hypotension. (See WARNINGS.) The dosage of ZESTRIL should be adjusted according to blood pressure response. If the patient's blood pressure is not controlled with ZESTRIL alone, diuretic therapy may be resumed as described above. If the diuretic cannot be discontinued, an initial dose of 5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.) Concomitant administration of ZESTRIL with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium. (See PRECAUTIONS.) **Use in Elderly:** In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of ZESTRIL. Pharmacokinetic studies, however, indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients so that dosage adjustments should be made with particular caution. **Dosage Adjustment in Renal Impairment:** The usual dose of ZESTRIL (10 mg) is recommended for patients with creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≥ 10 mL/min ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 5 mg once daily. For patients with creatinine clearance < 10 mL/min (usually on hemodialysis) the recommended initial dose is 2.5 mg. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Renal Status	Creatinine Clearance mL/min	Initial Dose mg/day
Normal Renal Function to Mild Impairment	>30	10
Moderate to Severe Impairment	≥10 ≤30	5
Dialysis Patients	<10	2.5‡

‡Dosage or dosing interval should be adjusted depending on the blood pressure response.

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Results of Percutaneous Transluminal Coronary Angioplasty in Patients ≥65 Years of Age (from the 1985 to 1986 National Heart, Lung, and Blood Institute's Coronary Angioplasty Registry)

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The 1985 to 1986 National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty (PTCA) Registry series of 1,801 initial procedures included 486 patients age ≥65 years (elderly). In comparison to younger patients, a greater proportion of elderly patients were women and had unstable angina. Elderly patients had more history of hypertension and more history of congestive heart failure. Although the elderly had more extensive vessel disease, the numbers of lesions and vessels attempted with PTCA were similar in the older and younger cohorts. Angiographic success rates were similar for all age groups. Although complication rates in the catheterization laboratory did not differ, patients ≥65 years were much more likely to require emergency coronary artery bypass graft surgery (CABG) (5.4 vs 2.8%, p <0.05) or elective CABG (3.9 vs 1.6%, p <0.01). The in-hospital death rate was considerably higher among the elderly (3.1 vs 0.2%, p <0.01). At 2-year follow-up, symptomatic status and cumulative rates of myocardial infarction, CABG and repeat PTCA were similar for elderly and younger patients. The death rate after 2 years was higher among elderly patients (8.8% of patients ≥65 years vs 2.9% of patients <65 years, p <0.01). When the relative risk of death for the elderly was adjusted for factors more prevalent among those ≥65 years (history of congestive heart failure, multivessel disease, unstable angina, history of hypertension and female gender), the relative risk remained significant but was substantially reduced (from 3.3 to 2.4).

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*See Appendix.

Since its introduction in 1977, percutaneous transluminal coronary angioplasty (PTCA) has emerged as a major nonsurgical alternative to coronary artery bypass graft surgery (CABG). An initial contraindication for PTCA was age ≥60 years.[1] Although early success rates were lower and complication rates were higher in the elderly compared to younger patients,[2] the results were sufficiently satisfactory that the use of PTCA in the elderly expanded. With increased life expectancy and continuing high prevalence of coronary artery disease, evaluation of PTCA in elderly patients is important.

The National Heart, Lung, and Blood Institute (NHLBI) established a voluntary PTCA registry in 1979. Twelve percent of the 3,079 patients entered were ≥65 years (elderly) and 1% were ≥75 years (very elderly). In that cohort, patients ≥65 years had a success rate of 53% compared to a rate of 62% among younger patients, and the elderly had a higher in-hospital mortality rate and a higher rate of elective CABG.[3] Because of rapid advances in PTCA technology and expanding indications for the procedure, the registry was reopened in 1985 to examine results under these new conditions.[4] The newer registry included a greater percentage of older patients. Twenty-seven percent of patients in the 1985 to 1986 registry were elderly and 12% were very elderly. This report compares risk profiles of elderly and very elderly patients to younger patients in the 1985 to 1986 cohort. In addition, we examined whether elderly patients were at higher risk of mortality and morbidity within 2 years of their first PTCA due purely to the higher prevalence of cardiovascular risk factors in these age groups, or whether advanced age was a risk over and above other characteristics of the elderly patients.

METHODS

The 1985 to 1986 NHLBI PTCA Registry collected data from 16 clinical centers that participated in the earlier registry. Data on characteristics and initial baseline results were collected on consecutive, first PTCA cases at each center. Follow-up information was obtained in an annual telephone interview. Patients will be followed for 5 years. The data were compiled, managed and analyzed at the Data Coordinating Center at the University of Pittsburgh.

TABLE I Baseline Characteristics by Age

	Age (yrs)		
	<65 (n = 1,315) (%)	65–74 (n = 394) (%)	≥75 (n = 92) (%)
Risk factors			
Female sex*	21	39	46
History of hypertension*	44	54	57
History of total cholesterol ≥250 mg/dl*	37	31	21
History of family coronary artery disease*	53	40	29
Current cigarette smoker*	36	15	5
History of diabetes mellitus	12	18	11
Clinical presentation			
Unstable angina*	48	54	58
Prior bypass surgery	12	16	4
Prior myocardial infarction	37	40	28
History of congestive heart failure*	4	9	17
Inoperable or high surgical risk*	6	12	22
Angiographic profile			
No. coronary arteries narrowed >50% in diameter by angiography†			
1	49	40	35
2	30	33	37
3	19	25	26
Left main	2	2	2
Left dominance	16	16	21
Ejection fraction <50%	18	21	22

* $p < 0.01$ for chi-square test of linear trend for age. † $p < 0.01$ for chi-square test of linear trend for age comparing 1- vs multiple-vessel disease (1 vs 2 or 3 narrowed arteries).

Registry definitions of success and complications established during the original period of the Registry have been reported.[4,5] Briefly, angiographic success was defined as a reduction of stenosis by ≥20% in all narrowings attempted and in-hospital clinical success was defined as angiographic success without in-hospital death, myocardial infarction or CABG. All infarctions were documented by ≥2 of the following: clinical symptoms, electrocardiographic evidence and enzyme changes. Patients were considered to have angina at 2 years if, during a structured telephone interview, they reported its occurrence within the previous month. Patients were classified as receiving maintenance medical therapy when they reported taking β blockers, calcium antagonists or long-acting nitrates on a regular daily basis at the time of the annual follow-up contact. Therapy at 2 years was classified into the following categories, ranging from least to most aggressive: no therapy, sublingual nitroglycerin without other medication, maintenance therapy, repeat angioplasty, bypass surgery, and both repeat angioplasty and bypass surgery.

The cohort of this study comprised 1,801 patients, of whom 486 were aged ≥65 years and 92 aged ≥75 years. Two-year follow-up data were available on 97% of the cohort. Patients were divided into 3 groups according to age: those <65 years, those between 65 and 74 years and those ≥75 years. The 3 groups were compared according to baseline medical history and coronary artery disease, risk factors, initial success and complications, and status at 2 years after PTCA. Further analysis was performed to determine if ≥65 years was an independent predictor of morbidity and mortality at 2 years. Logistic regression using maximum likelihood estimation was used to model the log odds of death and myocardial infarction. Coefficients were transformed to the odds scale for interpretation as an estimate of the risk of an event in the group of patients ≥65 years, relative to the risk of the event in a group of patients <65 years.

RESULTS

The elderly had a substantially different coronary artery disease risk profile compared with younger patients (Table I). The elderly and, in particular, the very elderly were significantly more likely to be women ($p < 0.01$) and have a history of hypertension ($p < 0.01$). On the other hand, the younger cohort was significantly more likely to have a history of high cholesterol ($p < 0.01$), a family history of coronary artery disease before age 55 ($p < 0.01$) and be smokers at the time of initial PTCA ($p < 0.01$). The prevalence of a history of diabetes was similar among patients <65 and ≥75, but higher among patients between ages 65 and 74.

The clinical presentation differed by age. The elderly were more likely to have unstable angina than younger patients and there was a significant linear trend with age. Additionally, among patients with unstable angina, the elderly, including the very elderly, were significantly more likely than patients <65 to have acute coronary insufficiency (transient ST or T-wave changes without development of Q waves) (40 vs 33%, $p < 0.05$), angina at rest (80 vs 67%, $p < 0.01$) and angina refractory to

TABLE II Attempted Lesion Characteristics by Age

No. of Narrowings Attempted	Age (yrs) <65 (n = 2,084) (%)	65–74 (n = 656) (%)	≥75 (n = 151) (%)
Single discrete morphology	59	56	54
Eccentric geometry	45	44	46
Calcium in stenosis*	10	17	20
Evidence of thrombosis	7	8	7
Total occlusion	11	10	9

* p <0.01 for chi-square test of linear trend for age.

TABLE III Procedural Characteristics by Age

	Age (yrs) <65 (n = 1,315) (%)	65–74 (n = 394) (%)	≥75 (n = 92) (%)
Brachial approach*	6	8	11
Staged procedure	4	6	7
Urgent or emergency procedure†	15	18	30
Two or more narrowings attempted	39	42	44
Two or more arteries attempted	21	26	25

* p <0.05 for chi-square test of linear trend for age; † p <0.01 for chi-square test of linear trend for age.

medical therapy (49 vs 41%, p <0.05) (not shown). The older cohort was significantly less likely to have new-onset angina (56 vs 63%, p <0.05). Among patients with stable angina, elderly patients were also more symptomatic than younger patients as measured by the Canadian Cardiovascular Society Classification, with 61% of the elderly and 50% of the younger patients in categories III or IV (p <0.01). Prior CABG was notably less frequent among the very elderly compared to patients <75 years. No significant differences were found between age groups regarding prior myocardial infarction. The elderly were more likely to have a history of congestive heart failure (p <0.01) and more likely to be judged a poor surgical candidate.

Elderly patients had more extensive vessel disease (i.e., more coronary arteries with ≥50% narrowing). Left main artery disease, generally a contraindication for PTCA, was present in just 2% of each age group. Although a slightly larger percentage of elderly patients had an ejection fraction <50% compared to the younger patients (21 vs 18%), the mean ejection fraction was the same, 59%. In all age groups, 6% of patients had low ejection fraction and 3-vessel disease.

Elderly patients had more attempted lesions with calcium in the stenosis (p <0.01) but few other baseline differences were found in attempted lesions between the elderly and nonelderly (Table II). There were no significant differences between age groups by lesion morphology, geometry, evidence of thrombosis, or receiving or supplying collateral vessels. Elderly patients had similar numbers of narrowings and arteries attempted by comparison with the younger cohort, but they were more likely to have procedures performed under urgent or emergency circumstances (p <0.01) (Table III). The brachial approach was more often attempted in the elderly cohort (p <0.05).

Among complications in the catheterization laboratory, coronary spasm occurred significantly more often among elderly patients (p <0.05) (Table IV). Rates of coronary occlusion were similar, whereas coronary dissection was somewhat less frequent among the elderly. By contrast, the elderly had significantly higher rates of emergency CABG (p <0.05) and elective CABG (p <0.01). Although there was not a significant difference in the incidence of myocardial infarction between the elderly and the younger cohort, the percentage for the very elderly was notably high. Perhaps the most striking difference between the elderly and patients <65 years was the in-hospital death rate (3.3% for the very elderly, 3.0% for those aged 65 to 74 and 0.2% for those <65 years, p <0.01). Of the 18 patients who died in-hospital after PTCA, 15 (83%) were elderly, even though less than one-third of all patients were elderly.

Table IV lists 2 measures of success used in the Registry. For angiographic success as measured by all narrowings dilated ≥20%, the elderly did about the same as the younger patients. For the second measure shown—all lesions successfully dilated without death, myocardial infarction or CABG (clinical success)—the elderly were at a slight disadvantage. Clinical success rates were 79% for patients <65 years, 76% for patients 65 to 74 years and 72% for patients ≥75 years.

At 2-year follow-up (Table V), the death rate was much higher among elderly patients (8.8% of patients ≥65 years vs 2.9% of patients <65 years, p <0.01). However, within the elderly cohort, mortality differed according to other risk factors. Mortality was 12% for women ≥65 but only 7% for men; for the elderly with multivessel disease the rate was 11% compared to 6% among elderly patients with 1-vessel disease.

Table V also shows that the cumulative rates of myocardial infarction, CABG and repeat PTCA were similar for elderly and younger patients. Presence of angina 2 years after initial PTCA was remarkably similar with slightly fewer than 25% of all patients, young and old, reporting angina. Elderly patients alive at 2 years tended to have more severe therapy implemented. In particular, there were fewer patients ≥75 who required no therapy—5%—compared to 15% among those 65 to 74 years old and 23% among the youngest group. Conversely, more of the elderly were receiving maintenance therapy.

Logistic regression models were used to examine the risk of an event for patients ≥65 years relative to the risk of the event for patients <65 years. For the event mortality or myocardial infarction within 2 years after PTCA, the relative risk for the elderly was 1.5. This increased risk of death or myocardial infarction was statistically significant (p <0.05). When other risk factors were included as explanatory variables, the effect of age, per se, was diminished. Adjustment for history of

TABLE IV In-Hospital Results by Age

Complications	Age (yrs) <65 (n = 1,315) (%)	65–74 (n = 394) (%)	≥75 (n = 92) (%)
None†	79.7	75.4	70.7
In laboratory			
Coronary spasm*	0.9	2.3	2.2
Coronary occlusion	4.9	4.8	4.3
Branch occlusion	2.0	2.8	1.1
Coronary dissection	5.2	3.8	2.2
Ventricular fibrillation	1.2	0.5	3.3
Out of laboratory			
Abrupt closure	2.1	3.0	0.0
Prolonged angina	4.2	5.6	7.6
Entry site complication	3.2	4.1	4.3
Major events			
Surgery			
Emergency CABG*	2.8	5.3	5.4
Elective CABG†	1.6	3.8	4.3
Myocardial infarction	4.5	4.6	8.7
Death†	0.2	3.0	3.3
Angiographic and clinical success			
All narrowings dilated ≥20%	83	81	80
All narrowings dilated ≥20% and no in-hospital death, myocardial infarction or CABG*	79	76	72

* $p < 0.05$ for chi-square test of linear trend for age; † $p < 0.01$ for chi-square test of linear trend for age.
CABG = coronary artery bypass graft surgery.

TABLE V Status at Two Years by Age

	Age (yrs) <65 (n = 1,315) (%)	65–74 (n = 394) (%)	≥75 (n = 92) (%)
Events			
Death*	3	8	13
Myocardial infarction	9	8	13
CABG	14	18	14
Repeat PTCA	22	19	20
Angina	24	23	22
Most Severe Therapy†	(n = 1,227)	(n = 353)	(n = 77)
None	23	15	5
Nitroglycerin only	1	1	0
Maintenance	44	51	57
Repeat PTCA only	18	16	22
CABG only	10	12	14
Repeat PTCA and CABG	4	4	1

* $p < 0.01$ for chi-square test of linear trend for age; † $p < 0.01$ for chi-square test.
CABG = coronary artery bypass graft surgery; PTCA = percutaneous transluminal coronary angioplasty.

congestive heart failure reduced the relative risk for the elderly to 1.3. Further adjustment for multivessel disease, female gender, unstable angina and history of hypertension reduced the relative risk for death or myocardial infarction for those ≥65 years compared to those <65 years to 1.2, a risk that was not statistically significant. When the event was mortality alone, the elderly were at a considerably increased risk and were more than 3 times more likely to die within 2 years of initial PTCA. When the risk of death for the elderly was adjusted for other factors that were more prevalent among those over 65 (history of congestive heart failure, multivessel disease, female gender, unstable angina and history of hypertension), the relative risk was reduced. However, the relative risk remained statistically significant at 2.4, which indicates that age was an independent risk factor for mortality in the Registry.

DISCUSSION

In the 1985 to 1986 NHLBI PTCA Registry, the percentage of patients ≥65 years with all attempted narrowings successfully dilated was 80%, whereas it was 83% in the younger group. This similarity of angiographic results was even more remarkable when we consider that the elderly group differed from the younger group with respect to many factors, including a greater proportion of women, higher prevalence of unstable angina and a greater proportion of patients with multivessel disease. Two years after the initial procedure, 77% of the elderly were free of angina compared to a similar rate of 76% among the younger cohort.

The differential mortality results of the elderly in relation to the younger group in the 1985 to 1986 cohorts were similar to the differential observed in the early Registry. In the 1977 to 1981 group, early mortality was 2.2% for the elderly compared to 0.7% for the younger group. In the recent cohort, the parallel rates were 3.2 and 0.2%. Mortality at 2 years in the 1977 to 1981 group was 5.2% for the elderly and 2.9% for the younger group. The recent cohort has a considerably worse cardiovascular disease profile and accordingly the 2-year mortality is 9% in the elderly.

A series of 54 patients with unstable angina age ≥60 performed between November 1980 and November 1985 was reported by Holt et al.[6] There were no in-

hospital deaths but 4 had occurred at an average of 37 months of follow-up. This cohort, however, consisted of 63% of patients with 1-vessel disease. During a similar time period, May 1980 to May 1984, 119 patients ≥65 years undergoing PTCA were reported by Raizner et al.[7] Among these patients, 79% of whom had 1-vessel disease, there was 1 in-hospital death and 4 late deaths, none from cardiac causes. Higher mortality rates among the elderly in our more recent cohort must be interpreted in the face of the worse risk factor status of these patients. For example, in the 1985 to 1986 Registry cohort, 65% of elderly patients had multivessel disease compared to only 35% of elderly patients with multivessel disease in the early cohort. The more recent elderly cohort also included 14% who were judged inoperable or high surgical risks. The early Registry did not record similar data but it is almost certain that there was a much smaller proportion of patients judged poor surgical candidates.

Multivariate statistical models show that the relative risk for the combined outcome of myocardial infarction or death within 2 years of PTCA for elderly patients is not significant when other risk factors are taken into account. Whereas adjustment for other risk factors does reduce the relative risk for the elderly for mortality alone, higher mortality among elderly patients cannot be explained completely by risk factors associated with age. The majority of deaths were cardiac related, but during follow-up there were 4 cancer deaths and 6 deaths of other noncardiac causes. The proportion of late deaths known to be of other than cardiac cause was slightly greater among the elderly (23%) than among the younger patients (16%).

The Registry allows a comparison of PTCA in elderly patients to younger patients, but a more relevant comparison is how the elderly fare with other treatments compared to PTCA. A major question that cannot be answered by this study is a comparison of these results to elderly patients undergoing CABG. Among published studies of elderly patients, earlier CABG series report higher perioperative mortality than more recent post-PTCA rates. Faro et al[8] report CABG operative mortality of 10.5% for patients >70 between 1974 and 1980. In 1982, Hochberg et al[9] examined the results for 75 patients ≥70 years. Operative mortality was 12% and an additional 3% died during an average of 22 months of follow-up. In the Coronary Artery Surgery Study Registry, there were 2,144 patients aged ≥65, of whom 1,086 underwent CABG.[10] Operative mortality was 5.2% for those ≥65 and 9.5% for those ≥75. Among 228 patients ≥70 years who underwent surgery between 1980 and 1984, Horneffer et al[11] reported operative mortality of 9.3% compared to 2.2% in those <70. Elderly patients discharged alive in the study had no increased risk of death during an average 30-month follow-up. In 1989, Mukherjee et al[12] reported case series to compare 102 patients >70 years who underwent CABG and 104 patients >70 years who underwent PTCA. In-hospital mortality was 7.8% for CABG and 1.9% for PTCA. The PTCA patients had a lower risk profile but CABG patients appeared to have a worse outcome, even when the differences in risk were taken into account.

Valid, unbiased comparisons of CABG and PTCA will be addressed by the Bypass Angioplasty Revascularization Investigation, which includes symptomatic patients up to 80 years of age with multivessel disease who are candidates for both revascularization procedures. Patients are assigned at random to an initial strategy of PTCA or CABG. Until the results of the clinical trials that compare PTCA with CABG or compare PTCA with medical therapy are available, we must rely on such data as are reported in the PTCA Registry to evaluate the results of PTCA in the elderly. There is no reported evidence that the mortality risk in elderly patients receiving PTCA is greater than that for patients in this age group treated with CABG. Given the current high success rates and low rates of nonfatal complications, PTCA is an attractive therapy for the elderly.

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APPENDIX

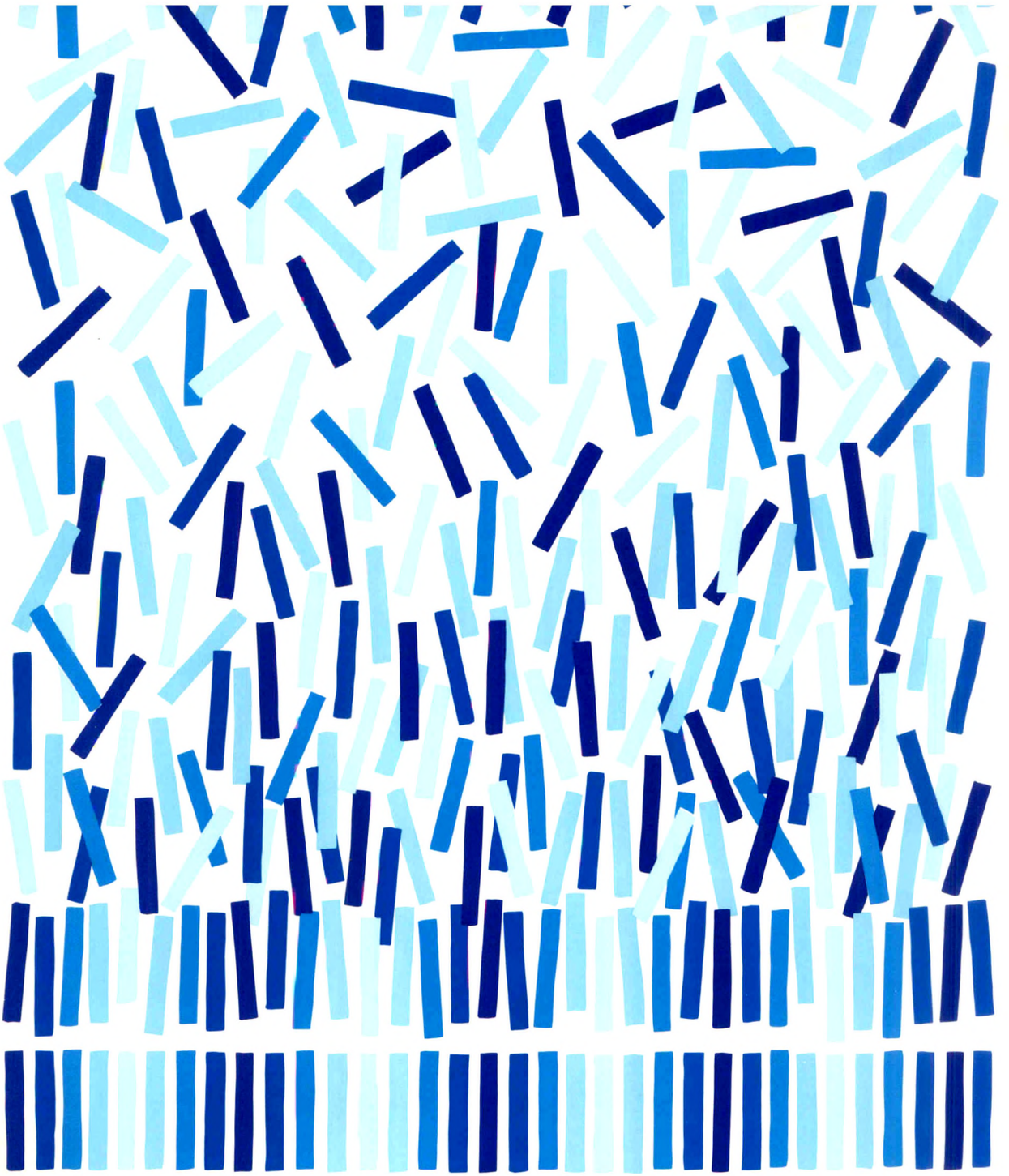
The following people and institutions participated in the National Heart, Lung, and Blood Institute's 1985 to 1986 Percutaneous Transluminal Coronary Angioplasty Registry.

Clinical Centers: *Boston University Medical Center/University Hospital* (*Boston, Massachusetts*)—David P. Faxon, MD,* Mirle A. Kellett, MD† (former), Timothy Sanborn, MD† (former), Alice K. Jacobs, MD,† and Madeline Erario‡; *Emory University Hospital* (*Atlanta, Georgia*) (Because data from this center are currently being integrated into the new-registry database, this site was not included in the analysis.)—Spencer B. King III, MD,* John Douglas, MD,† and Cynthia Sutor‡; *Georgetown University Hospital* (*Washington, D.C.*)—Kenneth M. Kent, MD,* Carolyn Ewels,‡ and Katie Kehoe‡; *Massachusetts General Hospital* (*Boston*)—Peter C. Block, MD,* and Elizabeth Block‡; *Mayo Clinic* (*Rochester, Minnesota*)—David R. Holmes, Jr., MD,* Ronald E. Vlietstra, MD,† Guy S. Reeder, MD,† J.F. Bresnahan, MD,† D.R. Bresnahan, MD,† A.A. Bove, MD,† LaVon Hammes,‡ and Susy Brevig‡; *Medical Center Hospital* (*Houston, Texas*)—Mahdi Al-Bassam, MD,* and Debbie Lance‡; *Medical College of Pennsylvania* (*Philadelphia*)—Lamberto G. Bentivoglio, MS, MD,* and Eileen Shappell‡; *Medical College of Virginia* (*Richmond*)—Michael J. Cowley, MD,* George W. Vetrovec, MD,† Stephen A. Lewis, MD,† Germano DiSciascio, MD,† and Kim Kelly‡; *Miami Heart Institute* (*Miami, Florida*)—Arthur J. Gosselin, MD,* Paul S. Swaye, MD,† Paul A. Vignola, MD,† and Hazel Yon‡; *Montreal Heart Institute* (*Montreal*)—Martial G. Bourassa, MD,* Paul Robert David, MD* (former), Micheline Labbe,‡ and Claudette Faille‡; *National Heart, Lung, and Blood Institute* (*Bethesda, Maryland*)—Richard O. Cannon, MD,* Martin Leon, MD,* and Rita Mincemoyer‡; *Seton Medical Center* (*Daly City, California*)—Richard K. Myler, MD,* Simon H. Stertzer, MD,* David A. Clark, MD,* and Mary Murphy‡; *Rhode Island Hospital/Brown University* (*Providence, Rhode Island*)—David O. Williams, MD,* and Shirley Emin‡; *St. Francis Regional Medical Center* (*Wichita, Kansas*)—Joseph P. Galichia, MD,* and Jan Meires‡; *St. Luke's Episcopal Hospital* (*Houston, Texas*)—Louis L. Leatherman, MD,* Arthur J. Springer, MD,†, and Joan Matties‡; *St. Luke's Hospital* (*Milwaukee, Wisconsin*)—Gerald Dorros, MD,* Lynne Janke-Mathiak‡, and Marla Engel.

Data Coordinating Center: *University of Pittsburgh* (*Pittsburgh*)—Katherine M. Detre, MD, DrPH,* Sheryl F. Kelsey, PhD,* John Wilson, PhD, Richard Holubkov, MS, Ann Rodewald Steenkiste, MS, and Ann Lu, MS (statisticians); William P. Amoroso (systems analyst); Sheela Ghosal (programmer); Verna Niedermeyer (data manager); Polly Swanson, Sharon Yeh, Huiman Xia Barnhart (research assistants); Donna Gibbons (administrative secretary) and Rita Wolk (secretary).

National Heart, Lung, and Blood Institute (*Bethesda*)—Louis Offen, MD (program office).

*Principal Investigator; †Associate Investigator; ‡Data Coordinator.



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Dizziness	12.5	2.4
Nausea/Vomiting	10.7	3.4
Unusual Taste	8.8	0.7
Constipation	7.2	0.5
Fatigue	6.0	1.0
Most Serious Adverse Events		
Proarrhythmia	4.7	
Congestive Heart Failure	3.7	
Third Degree AV Block	0.2	

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Patient selection

Indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that in the judgment of the physician, are life-threatening. There is no evidence from controlled trials that the use of any antiarrhythmic agent favorably affects survival or the incidence of sudden death. Therefore the use of Rythmol should be reserved for patients whom in the opinion of the physician the benefits of treatment outweigh the risks.

Rythmol and the CAST results

Although Rythmol was not included in CAST, the applicability of the Cardiac Arrhythmia Suppression Trial results to other populations (e.g., those without recent myocardial infarction), to Rythmol, or to other antiarrhythmic drugs is uncertain, but at present it is prudent to consider any 1C agent, such as Rythmol to have a similar risk.

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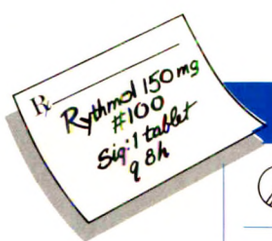
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CONTRAINDICATIONS

RYTHMOL (propafenone HCl) is contraindicated in the presence of uncontrolled congestive heart failure, cardiogenic shock, sinoatrial, atrioventricular and intraventricular disorders of impulse generation and/or conduction (e.g., sick sinus node syndrome, atrioventricular block) in the absence of an artificial pacemaker, bradycardia, marked hypotension, bronchospastic disorders, manifest electrolyte imbalance, and known hypersensitivity to the drug.

WARNINGS:

Mortality: In the National Heart Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a longterm, multicenter, randomized, double blind study in patients with asymptomatic non life threatening ventricular ectopy who had a myocardial infarction more than six days but less than two years previously and demonstrated mild to moderate left ventricular dysfunction, an excessive mortality or nonfatal cardiac arrest rate was seen in patients treated with encainide or flecainide (56/730) compared with that seen in patients assigned to carefully matched placebo treated groups (22/725). The average duration of treatment with encainide or flecainide in this study was ten months.The applicability of these results to other populations (e.g., those without recent myocardial infarction and to other antiarrhythmic drugs) is uncertain, but at present it is prudent (1) to consider any IC agent (especially one documented to provoke new serious arrhythmias) to have a similar risk and (2) to consider the risks of Class IC agents, coupled with the lack of any evidence of improved survival, generally unacceptable in patients without life threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life threatening, symptoms or signs.

Proarrhythmic Effects

RYTHMOL, like other antiarrhythmic agents, may cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia, ventricular fibrillation or torsade de pointes; i.e., tachycardia that is more sustained or more rapid which may lead to fatal consequences. It is therefore essential that each patient given RYTHMOL be evaluated electrocardiographically and clinically prior to, and during therapy to determine whether the response to RYTHMOL (propafenone HCl) supports continued treatment.Overall in clinical trials with propafenone, 4.7% of all patients had new or worsened ventricular arrhythmia possibly representing a proarrhythmic event (0.7% was an increase in PVCs; 4.0% a worsening, or new appearance, of VT or VF). Of the patients who had a worsening of VT (4%), 92% had a history of VT and/or VT/VF, 71% had coronary artery disease, and 68% had a prior myocardial infarction. The incidence of proarrhythmia in patients with less serious or benign arrhythmias, which include patients with an increase in frequency of PVCs, was 1.6%. Although most proarrhythmic events occurred during the first week of therapy, late events also were seen and the CAST study (see above) suggests that an increased risk is present throughout treatment.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)

PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE PROPAFENONE or other agents with beta adrenergic blocking activity.

Congestive Heart Failure

During treatment with oral propafenone in patients with depressed baseline function (mean EF=33.5%), no significant decreases in ejection fraction were seen. In clinical trial experience, new or worsened CHF has been reported in 3.7% of patients; of those 0.9% were considered probably or definitely related to RYTHMOL. Of the patients with congestive heart failure probably related to propafenone, 80% had preexisting heart failure and 85% had coronary artery disease. CHF attributable to RYTHMOL developed rarely (<0.2%) in patients who had no previous history of CHF. As RYTHMOL exerts both beta blockade and a (dose related) negative inotropic effect on cardiac muscle, patients with congestive heart failure should be fully compensated before receiving RYTHMOL. If congestive heart failure worsens, RYTHMOL should be discontinued (unless congestive heart failure is due to the cardiac arrhythmia) and, if indicated, restarted at a lower dosage only after adequate cardiac compensation has been established.

Conduction Disturbances

RYTHMOL slows atrioventricular conduction and also causes first degree AV block. Average PR interval prolongation and increases in QRS duration are closely correlated with dosage increases and concomitant increases in propafenone plasma concentrations. The incidence of first degree, second degree, and third degree AV block observed in 2,127 patients was 2.5%, 0.6%, and 0.2%, respectively. Development of second or third degree AV block requires a reduction in dosage or discontinuation of RYTHMOL. Bundle branch block (1.2%) and intraventricular conduction delay (1.1%) have been reported in patients receiving propafenone. Bradycardia has also been reported (1.5%). Experience in patients with sick sinus node syndrome is limited and these patients should not be treated with propafenone.

Effects on Pacemaker Threshold

RYTHMOL may alter both pacing and sensing thresholds of artificial pacemakers. Pacemakers should be monitored and programmed accordingly during therapy.

Hematologic Disturbances

One case of agranulocytosis with fever and sepsis, probably related to use of propafenone, was seen in U.S. clinical trials. The agranulocytosis appeared after 8 weeks of therapy. Propafenone therapy was stopped and the white count had normalized by 14 days. The patient recovered. In the course of over 800,000 patient years of exposure during marketing outside the U.S. since 1978, seven additional cases have been reported. In one of these, concomitant captopril, a drug known to cause agranulocytosis, was used. Unexplained fever and/or decrease in white cell count, particularly during the first three months of therapy, warrant consideration of possible agranulocytosis/granulocytopenia. Patients should be instructed to promptly report the development of any signs of infection such as fever, sore throat, or chills.

PRECAUTIONS

Hepatic Dysfunction:

Propafenone is highly metabolized by the liver and should, therefore, be administered cautiously to patients with impaired hepatic function. The dose of propafenone given to patients with impaired hepatic function should be significantly reduced. Careful monitoring for excessive pharmacological effects (see OVERDOSAGE) should be carried out.

Renal Dysfunction:

A considerable percentage of propafenone metabolites (18.5%-38% of the dose/48 hours) are excreted in the urine. Until further data are available, RYTHMOL should be administered cautiously to patients with impaired renal function. These patients should be carefully monitored for signs of overdosage (see OVERDOSAGE).

Elevated ANA Titers:

Positive ANA titers have been reported in patients receiving propafenone. Patients who develop an abnormal ANA test should be carefully evaluated and, if persistent or worsening elevation of ANA titers is detected, consideration should be given to discontinuing therapy.

Impaired Spermatogenesis:

Reversible disorders of spermatogenesis have been demonstrated in monkeys, dogs and rabbits after high dose intravenous administration. Evaluation of the effects of short term propafenone administration on spermatogenesis in 11 normal subjects suggests that propafenone produced a reversible, short term drop (within normal range) in sperm count. Subsequent evaluations in 11 patients receiving propafenone chronically have suggested no effect of propafenone on sperm count.

Drug Interactions: Quinidine: Small doses of quinidine completely inhibit the hydroxylation metabolic pathway, making all patients, in effect, slow metabolizers. There is, as yet, too little information to recommend concomitant use of propafenone and quinidine. **Local Anesthetics:** Concomitant use of local anesthetics may increase the risks of central nervous system side effects. **Digitalis:** RYTHMOL produces dose related increases in serum digoxin levels ranging from about 35% at 450 mg/day to 85% at 900 mg/day propafenone without affecting digoxin renal clearance. Digoxin dosage should ordinarily be reduced when propafenone is started. **Beta-Antagonists:** Propafenone appears to inhibit the hydroxylation pathway for propranolol and metoprolol (just as quinidine inhibits propafenone metabolism). While the therapeutic range for beta-blockers is wide, a reduction in dosage may be necessary during concomitant administration with propafenone. **Warfarin:** In a study of eight healthy subjects receiving propafenone and warfarin concomitantly, mean steady-state warfarin plasma concentrations increased 39% with a corresponding increase in prothrombin times of approximately 25%. It is therefore recommended that prothrombin times be routinely monitored and the dose of warfarin be adjusted if necessary. **Cimetidine:** Concomitant administration of propafenone and cimetidine in 12 healthy subjects resulted in a 20% increase in steady-state plasma concentrations of propafenone with no detectable changes in electrocardiographic parameters beyond that measured on propafenone alone. **Other:** Limited experience with propafenone combined with calcium antagonists and diuretics has been reported without evidence of clinically significant adverse reactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Life time maximally tolerated oral dose studies in mice (up to 360 mg/kg/day) and rats (up to 270 mg/kg/day) provided no evidence of a carcinogenic potential for propafenone. RYTHMOL was not mutagenic when assayed for genotoxicity. **Pregnancy Teratogenic Effects:** Pregnancy Category C.: Propafenone has been shown to be embryotoxic in rabbits and rats when given in doses 10 and 40 times, respectively, the maximum recommended human dose. No teratogenic potential was apparent in either species. There are no adequate and well controlled studies in pregnant women. Propafenone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Pregnancy Nonteratogenic Effects:** In a perinatal and postnatal study in rats, propafenone, at dose levels of 6 or more times the maximum recommended human dose, produced dose dependent increases in maternal and neonatal mortality, decreased maternal and pup body weight gain and reduced neonatal physiological development. **Labor and Delivery:** It is not known whether the use of propafenone during labor or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labor or increases the need for forceps delivery or other obstetrical intervention. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from RYTHMOL, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and efficacy of RYTHMOL in children has not been established.

Geriatric Use: There do not appear to be any age-related differences in adverse reaction rates in the most commonly reported adverse reactions. Because of the possible increased risk of impaired hepatic or renal function in this age group, RYTHMOL should be used with caution. The effective dose may be lower in these patients.

ADVERSE REACTIONS

Adverse reactions associated with RYTHMOL (propafenone HCl) occur most frequently in the gastrointestinal, cardiovascular, and central nervous systems. About 20% of patients discontinued due to adverse reactions.

Adverse reactions reported for ≥1% of 2,127 patients who received propafenone in U.S. clinical trials are presented in the following list. Dizziness, Nausea and/or Vomiting, Unusual Taste, Constipation, Fatigue, Dyspnea, Proarrhythmia, Angina, Headache(s), Blurred Vision, CHF, Ventricular Tachycardia, Dyspepsia, Palpitations, Rash, First Degree AV Block, Diarrhea, Weakness, Dry Mouth, Syncope/Near Syncope, Increased QRS Duration, Chest Pain, Anorexia, Abdominal Pain/Cramps, Ataxia, Insomnia, Premature Ventricular Contraction(s), Bradycardia, Anxiety, Edema, Tremor(s), Diaphoresis, Bundle Branch Block, Drowsiness, Atrial Fibrillation, Flatulence, Hypotension, Intraventricular Conduction Delay, Joint(s) Pain.

In addition, the following adverse reactions were reported less frequently than 1% either in clinical trials or in marketing experience *(adverse events for marketing experience are given in italics)*. Causality and relationship to propafenone therapy can not necessarily be judged from these events. **Cardiovascular System**: Atrial flutter, AV dissociation, cardiac arrest, flushing, hot flashes, sick sinus syndrome, sinus pause or arrest, supraventricular tachycardia. **Nervous System:** Abnormal dreams, abnormal speech, abnormal vision, *apnea, coma,* confusion, depression, memory loss, numbness, paresthesias, psychosis/mania, seizures (0.3%), tinnitus, unusual smell sensation, vertigo. **Gastrointestinal:** A number of patients with liver abnormalities associated with propafenone therapy have been reported in foreign postmarketing experience. Some appeared due to hepatocellular injury, some were cholestatic and some showed a mixed picture. Some of these reports were simply discovered through clinical chemistries, others because of clinical symptoms. One case was rechallenged with a positive outcome. Cholestasis (0.1%), elevated liver enzymes (alkaline phosphatase, serum transaminases) (0.2%), gastroenteritis, hepatitis (0.03%) **Hematologic**: Agranulocytosis, anemia, bruising, granulocytopenia, *increased bleeding time,* leukopenia, purpura, thrombocytopenia. **Other**: Alopecia, eye irritation, *hyponatremia/inappropriate ADH secretion,* impotence, increased glucose, *kidney failure,* positive ANA (0.7%), *lupus erythematosis,* muscle cramps, muscle weakness, nephrotic syndrome, pain, pruritus.

OVERDOSAGE

The symptoms of overdosage, which are usually most severe within 3 hours of ingestion, may include hypotension, somnolence, bradycardia, intraatrial and intraventricular conduction disturbances, and rarely convulsions and high grade ventricular arrhythmias. Defibrillation as well as infusion of dopamine and isoproterenol have been effective in controlling rhythm and blood pressure. Convulsions have been alleviated with intravenous diazepam. General supportive measures such as mechanical respiratory assistance and external cardiac massage may be necessary.

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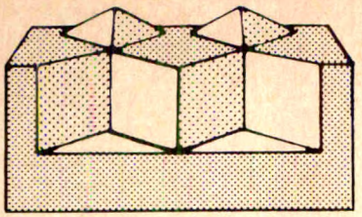
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Quantitative Angiographic Assessment of Elastic Recoil After Percutaneous Transluminal Coronary Angioplasty

Benno J. Rensing, MD, Walter R.M. Hermans, MD, Kevin J. Beatt, MD, Gert Jan Laarman, MD, Harry Suryapranata, MD, Marcel van den Brand, MD, Pim J. de Feyter, MD, and Patrick W. Serruys, MD, PhD

Little is known about the elastic behavior of the coronary vessel wall directly after percutaneous transluminal coronary angioplasty (PTCA). Minimal luminal cross-sectional areas of 151 successfully dilated lesions were studied in 136 patients during balloon inflation and directly after withdrawal of the balloon. To circumvent geometric assumptions about the shape of the stenosis after PTCA, a videodensitometric analysis technique was used for the assessment of vascular cross-sectional areas. Elastic recoil was defined as the difference between balloon cross-sectional area of the largest balloon used at the highest pressure and minimal luminal cross-sectional area after PTCA. Mean balloon cross-sectional area was 5.2 ± 1.6 mm² with a mean minimal cross-sectional area of 2.8 ± 1.4 mm² immediately after inflation. Oversizing of the balloon (balloon artery ratio >1) led to more recoil (0.8 ± 0.3 vs 0.6 ± 0.3 mm, p <0.001), suggestive of an elastic phenomenon. A difference in recoil of the 3 main coronary branches was observed: left anterior descending artery 2.7 ± 1.3 mm², circumflex artery 2.3 ± 1.2 mm² and right coronary artery 1.9 ± 1.5 mm² (p <0.025). The difference was still statistically significant if adjusted for reference area. Thus, nearly 50% of the theoretically achievable cross-sectional area (i.e., balloon cross-sectional area) is lost shortly after balloon deflation.

(Am J Cardiol 1990;66:1039–1044)

Percutaneous transluminal coronary angioplasty (PTCA) is increasingly being used as an alternative to coronary artery bypass grafting in patients with acute and chronically obstructed vessels.[1,2] Despite many publications on the mechanism of this treatment modality, little is known about the elastic behavior of the vessel wall during and immediately after angioplasty. Castaneda-Zuniga et al[3] proposed an arterial paralysis model in which overstretching of the vessel wall beyond its limits of elasticity was associated with histopathologic features of smooth muscle cell lysis. According to Sanborn et al,[4] part of the angioplasty mechanism consists of stretching the vessel wall resulting in a fusiform dilatation or localized aneurysm formation. It is, however, a common clinical observation that in some lesions even the application of an oversized balloon leads to a poor angiographic result without a visible intimal tear or dissection. This phenomenon may be attributed to elastic recoil of the vessel wall after balloon angioplasty. Densitometrically assessed cross-sectional areas are independent of geometric assumptions on the shape of the stenosis and should theoretically be more reliable than geometrically derived cross-sectional areas, especially after the disruptive action of balloon angioplasty which is known to cause asymmetric enlargement of the lumen.[5] This study was undertaken to determine the contribution of elastic recoil to the immediate result of an angioplasty procedure, with the use of densitometric and contour detection analysis techniques.

METHODS

Contour detection: The quantitative analysis of the stenotic coronary segments was performed with the computer-assisted Cardiovascular Angiography Analysis System (CAAS), which has been described in detail elsewhere.[6,7] To analyze a coronary arterial segment a 35-mm cine frame was selected. Electronically, a region of interest (512 × 512 pixels) encompassing the arterial segment to be analyzed was digitized with a high-fidelity videocamera. Contours of the arterial segments were detected automatically on the basis of the weighted sum of first and second derivative functions applied to the digitized brightness profile. From these contours the vessel diameter functions are determined by computing the shortest distance between the left and right contour positions (the upper curve in Figure 1). Conversion of the diameter measurements of the vessels to absolute values was achieved by using the contrast catheter as a

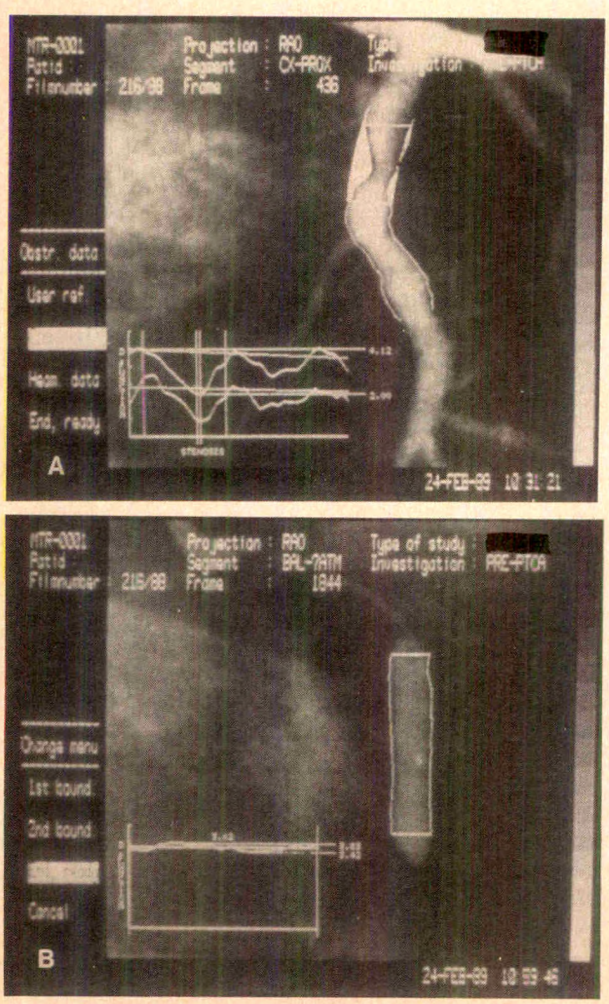
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scaling device. To this end the contours of a user-defined portion of the optimally magnified catheter (optimal magnification factor $2\sqrt{2}$) are detected automatically and corrected for pincushion distortion caused by the image intensifiers. In arteries with a focal obstructive lesion and a clearly normal proximal or distal arterial segment, the choice of the reference region is straightforward and simple. However, in cases where the proximal or distal part of the arterial segment shows combinations of stenotic and ectatic areas, the choice may become difficult. To circumvent these problems, we implemented a method that is independent on a user defined reference region. This technique is denoted "interpolated reference diameter measurement."[8] The principle of this technique is the computer estimation of the original vessel diameter at the site of obstruction (Figure 1). The white areas in the figure are measures for the "atherosclerotic plaque" and are defined by the actual luminal contours and the reconstructed reference contours. The length of the obstruction site is determined from the diameter function on the basis of curvature analysis and expressed in millimeters. Using the reconstructed borders of the vessel wall, the computer can calculate a symmetry coefficient for the stenosis: a symmetrical lesion having a value of 1 and a severe eccentric lesion having a value of 0. Symmetry is defined as the coefficient of the left hand distance between the reconstructed and actual vessel contours and the right hand distance between reconstructed and actual contours at the site of obstruction. In this equation the largest distance between actual and reconstructed contours becomes the denominator. The curvature value at the obstruction site, as a measure for coronary bending, is computed as the average value of all the individual curvature values along the centerline of the coronary segment, with the curvature defined as the first derivative of the tangent as it moves along the centerline, which for a circle is equal to the reciprocal of the radius.

Densitometric procedure: Constitution of the relation between path length of the x-rays through the artery and the brightness value requires a detailed analysis of the complete x-ray/cine/video chain, including the film development process.[9] For the first part of the chain from the x-ray source to the output of the image intensifier, Lambert Beer's law is assumed to be valid for the x-ray absorption and certain models for the x-ray source and the image intensifier are applied. Sensitometric transfer functions were assessed from 21 calibrated density frames, which are processed photographically simultaneously with the coronary cine film. These 21 density frames are then exposed homogenously with a specially developed sensitometer having the same color temperature as the output screen of the image intensifier.

The contours of a selected arterial segment are detected as previously described. On each scanline perpen-



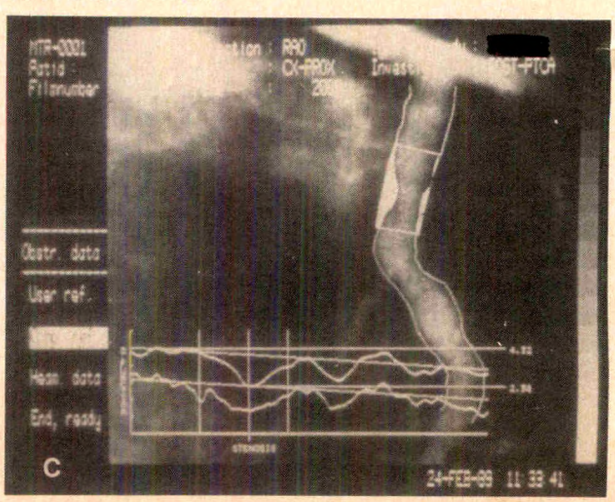


FIGURE 1. Single frame angiograms of a proximal, circumflex artery (CX-PROX). Contours and densitometric analysis of the severity of the obstruction (Obstr.). The white areas are a measure for the "atherosclerotic" plaque and are defined by the difference between the actual luminal contours and the "interpolated" reference contours. Superimposed on the videoimage are the diameter function curves *(upper curve)* and the densitometric area function curve *(lower curve)* together with the "interpolated reference" curves. *A*, predilatation (before percutaneous transluminal coronary angioplasty [PRE-PTCA]) minimal luminal cross-sectional area is 3.5 mm²; *B*, 3.5 mm balloon, filmed at highest inflation pressure; *C*, after dilatation (POST-PTCA), minimal luminal cross-sectional area is 6.0 mm².

dicular to the centerline a profile of brightness values is measured. This profile is transformed into an absorption profile by means of the computed transfer functions. The background contribution is estimated by an interpolative method and subtraction of this background yields the net cross-sectional absorption profile. Integration of this function results in a measure for the cross-sectional area at the particular scanline. By repeating this procedure for each scanline, the cross-sectional area function is obtained. The severity of the obstruction can thus be expressed in mm^2, by comparing the minimal area value at the obstruction with the reference value obtained after an interpolative approach, which is similar to that described earlier for diameter measurements.

Validation of this densitometric analysis technique was done by analyzing cine films of perspex models filled with a contrast agent and filmed at 4 kV levels. Accuracy was found to be 2.8% and precision 1.8%.[10] The densitometrically determined area stenosis, as found by other investigators, correlates well with percentage reduction of cross-sectional area measured histologically in postmortem hearts.[11,12]

Assessment of elastic recoil: One hundred fifty-one successfully dilated segments of 136 patients were analyzed. A successful PTCA was defined as a visually assessed diameter stenosis after PTCA of <50%. Single identical views before and after PTCA, and during complete expansion of the largest balloon at highest inflation pressure were chosen for densitometric analysis. Both polyvinyl chloride and polyethylene balloons were used for dilatation depending on the choice of the operator. Inflation pressure and duration of inflation were left to the discretion of the operator. Mean balloon cross-sectional areas were calculated from diameter values, assuming a circular cross section at maximal inflation pressure. The same x-ray setting in terms of kilovoltage and milliamperes was used during the 3 cine recordings. To have the segment to be analyzed as perpendicular to the incoming x-rays as possible, a view was chosen with the coronary artery appearing least foreshortened. The same amount of nitrates, either nitroglycerin, 0.1 to 0.3 mg, or isosorbide dinitrate, 1 to 3 mg, was given intracoronarily before the pre- and postangioplasty cine recordings. This was done to dilate the vessel maximally and thus to control the varying influence of vasomotor tone on luminal dimensions. Elastic recoil was then calculated as the difference between the minimal luminal cross-sectional area after PTCA and the mean balloon cross-sectional area (mm^2). A representative analysis, with the detected contours, the diameter function curve and the densitometric area function curve superimposed on the original video image, is shown in Figure 1 for a circumflex lesion.

RESULTS

At quantitative analysis 140 (92%) of the dilatations were successful using a <50% diameter stenosis after PTCA as the success criterion. If in addition a >20% improvement in diameter stenosis was required for a successful dilatation, 110 (72%) lesions were successfully dilated using quantitative measurements. The densitometric analysis of the 151 segments is listed in Table I. Mean age of the 136 patients was 56.8 ± 8 years. There was no significant change in "interpolated" reference area after PTCA: Before PTCA 6.0 ± 2.5 mm^2, after PTCA 6.2 ± 2.5 mm^2 (difference not significant). The minimal luminal cross-sectional area increased from 1.1 ± 0.9 to 2.8 ± 1.4 mm^2 ($p < 0.001$). The mean balloon cross-sectional area was 5.2 ± 1.6 mm^2. Elastic recoil was 2.4 ± 1.4 mm^2. Thus, nearly 50% of the theoretically achievable cross section (i.e., balloon cross-sectional area) was lost immediately after the last balloon deflation. A subset of 16 patients (18 lesions) were angiographically reexamined 24 hours after PTCA as part of a study looking at changes in coronary flow reserve in the first 24 hours after balloon dilatation. Minimal luminal cross-sectional area directly after PTCA in this group was 2.0 ± 0.8 mm^2 and 1.9 ± 0.5 at 24 hours (difference not significant).

Balloon oversizing and elastic recoil: For each stenotic lesion the balloon-artery ratio was calculated. A ratio >1 indicates oversizing of the balloon. The mean balloon-artery ratio in this study was 0.95 ± 0.18. This indicates a conservative balloon handling, considered to give optimal dilatation of the stenotic lesion with minimal residual stenosis and the smallest incidence of coro-

TABLE I Recoil in 151 Coronary Arterial Narrowings

	Before PTCA	After PTCA	p Value
Reference area (mm^2)	6.0 ± 2.5	6.2 ± 2.5	NS
MLCA (mm^2)	1.1 ± 0.9	2.8 ± 1.4	p <0.001
Balloon-CSA (mm^2)		5.2 ± 1.6	
Recoil (mm^2)		2.4 ± 1.4	p <0.001

CSA = cross-sectional area; MLCA = minimal luminal cross-sectional area; NS = difference not significant; PTCA = percutaneous transluminal coronary angioplasty; Recoil = balloon CSA − MLCA after PTCA.

TABLE II Effect of Balloon Oversizing on the Amount of Elastic Recoil

Balloon-Artery Ratio	≤1	>1	p Value
No. of lesions	87	64	
Reference-diameter (mm)	3.0 ± 0.5	2.3 ± 0.4	p <0.001
Balloon-diameter (mm)	2.5 ± 0.4	2.6 ± 0.4	NS
Recoil (mm)	0.6 ± 0.30	0.8 ± 0.3	p <0.001

Balloon-artery ratio = balloon diameter/reference diameter; NS = difference not significant.

TABLE III Clinical Characteristics and Recoil in 136 Patients

	Yes	No	p Value
Men (recoil)	112 (0.45 ± 0.31)	24 (0.42 ± 0.23)	NS
Smoking (recoil)	106 (0.46 ± 0.29)	30 (0.50 ± 0.23)	NS
Hypertension (recoil)	61 (0.40 ± 0.28)	75 (0.46 ± 0.29)	NS
Diabetes type 1 (recoil)	1	135	
Unstable angina (recoil)	23 (0.39 ± 0.27)	113 (0.44 ± 0.26)	NS

Recoil corrected for reference area.
NS = difference not significant.

TABLE IV Angiographic and Procedural Characteristics and Recoil of 151 Lesions

	Yes	No	p Value	Mean
Lesion length >5.2 mm and <7 mm (recoil)	50 (0.48 ± 0.25)	101 (0.43 ± 0.33)	NS	6.4 ± 2.4 mm
Calcified lesion (recoil)	22 (0.43 ± 0.29)	129 (0.45 ± 0.45)	NS	
Symmetry <0.37 (recoil)	51 (0.48 ± 0.33)	100 (0.41 ± 0.30)	p = 0.07	0.5 ± 0.3
Plaque area <4.5 mm^2 (recoil)	50 (0.53 ± 0.33)	101 (0.41 ± 0.27)	p <0.01	6.8 ± 3.9 mm^2
Curvature <12.5 units (recoil)	51 (0.53 ± 0.34)	100 (0.43 ± 0.31)	p <0.01	17.7 ± 10.4
Max. infl. pres. <8 atm (recoil)	49 (0.46 ± 0.24)	102 (0.46 ± 0.35)	NS	9.6 ± 2.5 atm
Inflation duration <220 seconds (recoil)	50 (0.47 ± 0.30)	101 (0.44 ± 0.29)	NS	309 ± 170 seconds

Recoil corrected for reference area. See text for description of cutoff points.
Max. infl. pres. = maximal inflation pressure of the balloon; NS = difference not significant.

TABLE V Recoil in the Three Main Coronary Arteries

	LAD (n = 77)	LC (n = 34)	Right (n = 40)	ANOVA
Balloon CSA (mm^2)	5.2 ± 1.7	5.5 ± 1.5	4.9 ± 1.4	NS
MLCA after PTCA (mm^2)	2.5 ± 1.3	3.1 ± 1.2	3.0 ± 1.7	NS
Recoil (mm^2)	2.7 ± 1.3	2.3 ± 1.2	1.9 ± 1.5	p <0.025
Recoil/reference area	0.5 ± 0.3	0.4 ± 0.2	0.3 ± 0.3	p <0.05

ANOVA = analysis of variance; CSA = cross-sectional area; LAD = left anterior descending artery; LC = left circumflex artery; MLCA = minimal luminal cross-sectional area; NS = difference not significant.

nary dissection.[13,14] Lesions with a ratio >1 (oversizing) were compared with lesions with a ratio ≤1. The comparative data are listed in Table II. No difference was found in balloon diameter between the groups. As expected, reference diameter was higher in the group with a ratio ≤1. Elastic recoil was more pronounced in the second group (0.84 ± 0.29 vs 0.64 ± 0.30 mm, p <0.001). Thus, oversizing of the balloon leads to more elastic recoil. These results agree with elastic phenomena: more stretch leads to more recoil (within limits of elasticity).

Clinical characteristics and recoil: Clinical characteristics and risk factors of the 136 patients are listed in Table III. No differences in elastic recoil were observed for gender, the presence or absence of risk factors and the presence or absence of unstable angina.

Quantitative angiographic lesion characteristics and recoil: Quantitative data on lesion morphology before angioplasty are listed in Table IV. To avoid arbitrary subdivision of data, cutoff criteria for lesion length, symmetry, plaque area and curvature value were derived by dividing the data in 3 groups so that each group contained about one-third of the population. The group with the highest amount of recoil was then compared with the 2 other groups. Lesions with a small plaque area and lesions with a shallow curvature showed significantly more recoil (Table IV).

Procedural related variables and recoil: Table IV lists the total inflation duration and maximal balloon inflation pressure in relation to elastic recoil. No differences in elastic recoil were observed.

Recoil in the three main coronary arteries: The amount of recoil was calculated in the left anterior descending artery (n = 77), the circumflex artery (n = 34) and in the right coronary artery (n = 40). Data are listed in Table V. The amount of recoil was significantly larger in the left anterior descending artery compared with the circumflex and right coronary arteries, 2.7, 2.3

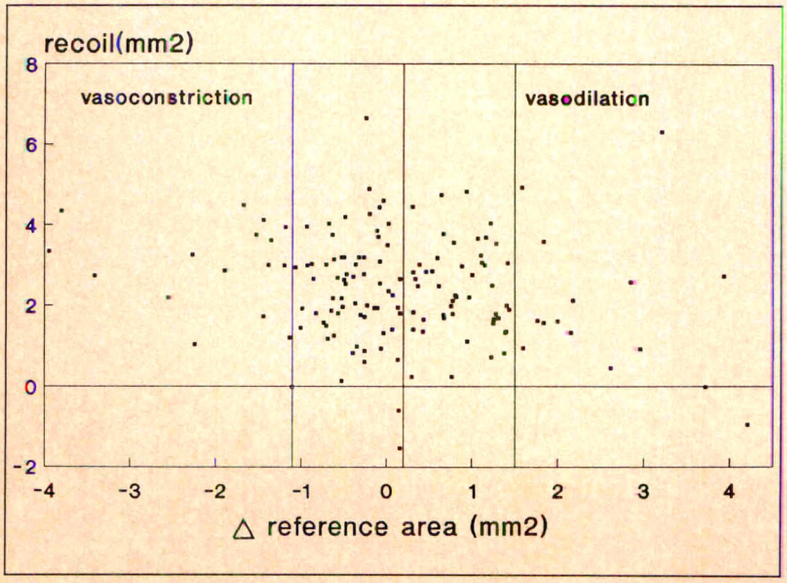


FIGURE 2. In this scatterplot the difference in interpolated reference area before and after percutaneous transluminal coronary angioplasty is plotted against the amount of recoil for each segment. The mean difference in reference area was 0.2 ± 1.3 mm^2 *(vertical lines in graph)*. The values are randomly distributed around the mean value of 0.2 mm^2, suggesting that spasm was effectively eliminated.

and 1.9 mm^2, respectively ($p < 0.025$). When normalized for reference area the difference was still statistically significant.

DISCUSSION

Vasoconstriction at the dilatation site is a common cause of early luminal narrowing. As has been shown elegantly by Fischell et al[15] this can be rapidly reversed by an intracoronary injection of nitrates. Because we gave intracoronary nitrates before the pre- and post-PTCA cine runs, it seems unlikely that the amount of recoil observed was caused by vasomotion. In Figure 2 the difference between the reference area before and after PTCA is plotted against the amount of recoil for each site. The values are randomly distributed around the mean value of 0.2 mm^2, suggesting the absence of vasoconstriction at the post-PTCA film.

Platelet deposition, and the formation of a nonocclusive mural thrombus despite full heparinization, is not an uncommon finding in postmortem hearts obtained from patients who die in the first hours after angioplasty.[16] This has also been confirmed by angioscopy 15 to 30 minutes after PTCA.[17] However, our post-PTCA angiograms were recorded within minutes of the last dilatation. Although we cannot rule out the possibility that mural thrombus formation is partly responsible for the observed phenomenon, we believe it cannot explain the 50% decrease in luminal area found. Subintimal hemorrhage is also a cause of severe early luminal narrowing or acute closure, a process which is usually impossible to reverse and nearly always results in a failed PTCA. In this study only successfully dilated lesions were analyzed.

The mean balloon cross-sectional area was derived over the total length of the balloon and compared with the minimal luminal cross-sectional area measured immediately after PTCA. In this study, recoil of the part of the dilated segment adjacent to this area was not specifically studied. We assumed a uniform expansion of the balloon at maximal inflation pressure. Theoretically, recoil should be assessed using the minimal luminal balloon cross-sectional area.

The 18 lesions restudied 24 hours after PTCA showed no difference in minimal luminal cross-sectional area with respect to the cross-sectional area directly after PTCA. This suggests that elastic recoil is an instantaneous phenomenon. This finding does not agree with the findings of Nobuyoshi et al,[18] who found a significant deterioration of minimal luminal diameter 1 day after PTCA. However, the small size of this subgroup may not be representative of the total population. A trend toward more recoil was observed in asymmetric lesions. In these lesions the balloon will preferrably stretch the nondiseased part of the vessel circumference with a subsequent larger elastic recoil.[19] The fact that a small plaque area and a low curvature value are attended with a significant higher amount of elastic recoil may be due to the fact that dissections have been found most often in areas containing thick atherosclerotic plaques and lesions with a high bending.[20,21] Gross disruption of the vessel wall may prevent the recoil phenomenon. Procedural variables had no influence on the amount of recoil. Longer inflations and higher inflation pressures are often used after an initially poor angioplasty result. Only a randomized trial can indicate to what extend procedural factors influence procedural outcome.

Jain et al[22] found, using an in vivo technique for obtaining balloon pressure-volume loops, a pattern consistent with stretching of the arterial wall in 56% of lesions. A pressure-volume loop consistent with stretching of the vessel was a far more common event than a cracking pattern (17%). Stretching within limits of elasticity implies its counterpart elastic recoil. More stretching should lead to more recoil. In our series, oversizing of the balloon (i.e., a balloon-artery ratio >1) was associated with more recoil, indicative of the elastic phenomenon. Dobrin described pressure radius curves of potassium cyanide–poisoned carotid arteries of mongrel dogs. At low pressures, the vessel exhibited large changes in radius with each step in pressure, whereas at high pressure it showed very slight changes in radius. The curve described an elastic hysteresis loop, with the ascending and descending limb close to each other at all pressures, suggesting no active muscle contraction involvement in the retraction process.[23]

The differences in elastic recoil observed in the 3 coronary arteries cannot be easily be explained. Differences in histologic structure or differences in plaque composition in the coronary arteries might be an explanation. To our knowledge these differences have not been reported.

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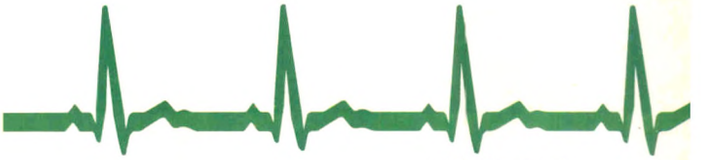
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The only antidote for digitalis intoxication*





(artist's interpretation)

Only one treatment removes the cause of digitalis intoxication.

Digibind.

Most patients show clinical signs of improvement within one hour of administration, and complete recovery usually occurs in about four hours.[1]

Safety data from a large post-marketing surveillance study (n = 745) show a less than 1% incidence of allergic reactions, and those reactions were not life threatening.[2]



In cases of potentially life-threatening digitalis intoxication, administer the only antidote – Digibind.

DIGIBIND®

DIGOXIN IMMUNE FAB (OVINE)

*Digibind is indicated for the treatment of potentially life-threatening digoxin intoxication. It has also been used successfully to treat life-threatening digitoxin overdose. Please see brief summary of prescribing information on the next page.

DIGIBIND®

DIGOXIN IMMUNE FAB (OVINE)

The only antidote for digitalis intoxication*

Before using, please consult complete product information, a summary of which follows:

INDICATIONS AND USAGE: Digibind, Digoxin Immune Fab (Ovine), is indicated for treatment of potentially life-threatening digoxin intoxication.[1] Although designed specifically to treat life-threatening digoxin overdose, it has also been used successfully to treat life-threatening digitoxin overdose.[1] Since human experience is limited and the consequences of repeated exposures are unknown, Digibind is not indicated for milder cases of digitalis toxicity.

Manifestations of life-threatening toxicity include severe ventricular arrhythmias such as ventricular tachycardia or ventricular fibrillation, or progressive bradyarrhythmias such as severe sinus bradycardia or second or third degree heart block not responsive to atropine.

Ingestion of more than 10 mg of digoxin in previously healthy adults or 4 mg of digoxin in previously healthy children, or ingestion causing steady-state serum concentrations greater than 10 ng/ml, often results in cardiac arrest. Digitalis-induced progressive elevation of the serum potassium concentration also suggests imminent cardiac arrest. If the potassium concentration exceeds 5 mEq/L in the setting of severe digitalis intoxication, Digibind therapy is indicated.

CONTRAINDICATIONS: There are no known contraindications to the use of Digibind.

WARNINGS: Suicidal ingestion often involves more than one drug; thus toxicity from other drugs should not be overlooked.

One should consider the possibility of anaphylactic, hypersensitivity or febrile reactions. If an anaphylactoid reaction occurs, the drug infusion should be discontinued and appropriate therapy initiated using aminophylline, oxygen, volume expansion, diphenhydramine, corticosteroids and airway management as indicated. The need for epinephrine should be balanced against its potential risk in the setting of digitalis toxicity.

Since the Fab fragment of the antibody lacks the antigenic determinants of the Fc fragment, it should pose less of an immunogenic threat to patients than does an intact immunoglobulin molecule. Patients with known allergies would be particularly at risk, as would individuals who have previously received antibodies or Fab fragments raised in sheep.

Skin testing for allergy was performed during the clinical investigation of Digibind. Only one patient developed erythema at the site of skin testing, with no accompanying wheal reaction; this individual had no adverse reaction to systemic treatment with Digibind. Since allergy testing can delay urgently needed therapy, it is not routinely required before treatment of life-threatening digitalis toxicity with Digibind.

Skin testing may be appropriate for high risk individuals, especially patients with known allergies or those previously treated with Digoxin Immune Fab (Ovine). The intradermal skin test can be performed by: 1. Diluting 0.1 ml of reconstituted Digibind (10 mg/ml) in 9.9 ml sterile isotonic saline (1:100 dilution, 100 μg/ml). 2. Inject 0.1 ml of the 1:100 dilution (10 μg) intradermally and observe for an urticarial wheal surrounded by a zone of erythema. The test should be read at 20 minutes.

The scratch test procedure is performed by placing one drop of a 1:100 dilution of Digibind on the skin and then making a ¼-inch scratch through the drop with a sterile needle. The scratch site is inspected at 20 minutes for an urticarial wheal surrounded by erythema.

If skin testing causes a systemic reaction, a tourniquet should be applied above the site of testing and measures to treat anaphylaxis should be instituted. Further administration of Digibind should be avoided unless its use is absolutely essential, in which case the patient should be pretreated with corticosteroids and diphenhydramine, and preparations made for treating anaphylaxis.

PRECAUTIONS:

General: Digoxin Immune Fab (Ovine) has been used on only a limited scale in man and its safety has therefore not yet been completely defined.

Standard therapy for digitalis intoxication includes withdrawal of the drug and correction of factors that may contribute to toxicity, such as electrolyte disturbances, hypoxia, acid-base disturbances and agents such as catecholamines. Also, treatment of arrhythmias may include judicious potassium supplements, lidocaine, phenytoin, procainamide and/or propranolol; treatment of sinus bradycardia or atrioventricular block may involve atropine or pacemaker insertion. Massive digitalis intoxication can cause hyperkalemia; administration of potassium supplements in the setting of massive intoxication may be hazardous (see Laboratory Tests). After treatment with Digibind, the serum potassium concentration may drop rapidly[2] and must be monitored frequently, especially over the first several hours after Digibind is given (see Laboratory Tests).

The elimination half-life in the setting of renal failure has not been clearly defined. Several patients with mild to moderate renal dysfunction have been successfully treated with Digibind.[3] There is no evidence to suggest the time course of therapeutic effect is any different in these patients than in patients with normal renal function, but excretion of the Fab fragment-digoxin complex from the body is probably delayed. In patients who are functionally anephric, one would anticipate failure to clear the Fab fragment-digoxin complex from the blood by glomerular filtration and renal excretion. In this setting the reticuloendothelial system might eliminate the complex. Whether this would lead to detoxification or to reintoxication following release of newly unbound digoxin into the blood is uncertain. Such patients should be monitored for a prolonged period for possible recurrence of digitalis toxicity.

Patients with intrinsically poor cardiac function may deteriorate from withdrawal of the inotropic action of digoxin. Studies in animals have shown that the reversal of inotropic effect is relatively gradual, occurring over hours. When needed, additional support can be provided by use of intravenous inotropes, such as dopamine or dobutamine, or vasodilators. One must be careful in using catecholamines not to aggravate digitalis toxic rhythm disturbances. Clearly, other types of digitalis glycosides should not be used in this setting.

Redigitalization should be postponed, if possible, until the Fab fragments have been eliminated from the body, which may require several days. Patients with impaired renal function may require a week or longer.

Laboratory Tests: Serum digoxin or digitoxin concentration should be obtained before Digibind administration if at all possible. These measurements may be difficult to interpret if drawn soon after the last digitalis dose, since at least 6 to 8 hours are required for equilibration of digoxin between serum and tissue. Patients should be closely monitored, including temperature, blood pressure, electrocardiogram and potassium concentration, during and after administration of Digibind. The total serum digoxin concentration may rise precipitously following administration of Digibind but this will be almost entirely bound to the Fab fragment and therefore not able to react with receptors in the body. Digibind will interfere with digitalis immunoassay measurements.[4] Thus, the standard serum digoxin concentration measurement can be clinically misleading until the Fab fragment is eliminated from the body, which may require several days. Patients with impaired renal function may require a week or longer before the standard serum digoxin concentration assay will give reliable results.

Potassium concentrations should be followed carefully. Severe digitalis intoxication can cause life-threatening elevation in serum potassium concentration by shifting potassium from inside to outside the cell. The elevation in serum potassium concentration can lead to increased renal excretion of potassium. Thus, these patients may have hyperkalemia with a total body deficit of potassium. When the effect of digitalis is reversed by Digibind, potassium shifts back inside the cell, with a resulting decline in serum potassium concentration.[3] Hypokalemia may thus develop rapidly. For these reasons, serum potassium concentration should be monitored repeatedly, especially over the first several hours after Digibind is given, and cautiously treated when necessary.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There have been no long-term studies performed in animals to evaluate carcinogenic potential.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with Digibind. It is also not known whether Digibind can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Digibind should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Digibind is administered to a nursing woman.

Pediatric Use: Digibind has been successfully used in infants with no apparent adverse sequelae. As in all other circumstances, use of this drug in infants should be based on careful consideration of the benefits of the drug balanced against the potential risk involved.

ADVERSE REACTIONS: Allergic reactions to Digibind have been reported rarely. Atopic patients appear to be at particular risk. In a few instances, low cardiac output states and congestive heart failure could have been exacerbated by withdrawal of the inotropic effects of digitalis. Hypokalemia may occur from re-activation of (sodium, potassium) ATPase (see Laboratory Tests). Patients with atrial fibrillation may develop a rapid ventricular response from withdrawal of the effects of digitalis on the atrioventricular node.[3]

DOSAGE AND ADMINISTRATION: Digibind, Digoxin Immune Fab (Ovine), is administered by the intravenous route over 30 minutes. It is recommended that it be infused through a 0.22 μm membrane filter. If cardiac arrest is imminent, it can be given as a bolus injection.

The dosage of Digibind varies according to the amount of digoxin to be neutralized. The average dose used during clinical testing was 10 vials. Dosing guidelines are given in the full product labeling. If after several hours toxicity has not adequately reversed or appears to recur, readministration of Digibind at a dose guided by clinical judgment may be required. If a patient presents with digitalis toxicity from an acute ingestion, and neither a serum digitalis concentration nor an estimated ingestion amount is available, 20 vials (800 mg) of Digibind can be administered. This amount will be adequate to treat most life-threatening ingestions in both adults and children. However, in small children it is important to monitor for volume overload. Failure to respond to Digibind raises the possibility that the clinical problem is not caused by digitalis intoxication. If there is no response to an adequate dose of Digibind, the diagnosis of digitalis toxicity should be questioned.

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***Digibind is indicated for treatment of potentially life-threatening digoxin intoxication. It has also been used successfully to treat life-threatening digitoxin overdose.**

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